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(71) Demandeur/Applicant:
PRESIDENT AND FELLOWS OF HARVARD COLLEGE, US

(72) Inventeurs/Inventors:
YUAN, JUNYING, US;
HSU, EMILY S., DE

(74) Agent: GOUDREAU GAGE DUBUC

(54) Titre : INHIBITEURS DE LA NECROPTOSE DE PETITE TAILLE MOLECULAIRE
(54) Title: SMALL MOLECULE INHIBITORS OF NECROPTOSIS

(57) Abrégé/Abstract:
The invention features a series of heterocyclic derivatives that inhibit tumor necrosis factor alpha (TNF-a) induced necroptosis. The heterocyclic compounds of the invention are described by Formulas (I)-(VIII) and by Compounds (I)-(I), (13)-(26), (27)-(33), (48)-(57), and (58)-(70). These necrostatins are shown to inhibit TNF-a induced necroptosis in FADD- deficient variant of human Jurkat T cells. The invention further features pharmaceutical compositions featuring necrostatins. The compounds and compositions of the invention may also be used to treat disorders where necroptosis is likely to play a substantial role.

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(71) Applicant *(for all designated States except US)*: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **YUAN, Junying** [US/US]; 22 Fairlee Road, Newton, MA 02468 (US). **HSU, Emily, S.** [US/DE]; Rolf-pinegger-strasse 4, 80689 Munich (DE).

(74) Agents: **BIEKER-BRADY, Kristina** et al.; Clark & Elbing LLP, 101 Federal Street, Boston, MA 02110 (US).

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(54) **Title**: SMALL MOLECULE INHIBITORS OF NECROPTOSIS

(57) **Abstract**: The invention features a series of heterocyclic derivatives that inhibit tumor necrosis factor alpha (TNF-α) induced necroptosis. The heterocyclic compounds of the invention are described by Formulas (I)-(VIII) and by Compounds (I)-(I), (13)-(26), (27)-(33), (48)-(57), and (58)-(70). These necrostatins are shown to inhibit TNF-α induced necroptosis in FADD- deficient variant of human Jurkat T cells. The invention further features pharmaceutical compositions featuring necrostatins. The compounds and compositions of the invention may also be used to treat disorders where necroptosis is likely to play a substantial role.

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SMALL MOLECULE INHIBITORS OF NECROPTOSIS

Cross-Reference to Related Applications

This application claims benefit of U.S. Provisional Application No. 61/140,615, filed December 23, 2008, which is hereby incorporated by reference.

Statement as to Federally Sponsored Research

This invention was made with government support under UO1 NS050560 awarded by the National Institutes of Health. The U.S. government has certain rights to this invention.

Field of the Invention

The invention relates to compounds and to cell death, in particular through necrosis and necroptosis, and regulation thereof by small molecules.

Background of the Invention

In many diseases, cell death is mediated through apoptotic and/or necrotic pathways. While much is known about the mechanisms of action that control apoptosis, control of necrosis is not as well understood. Understanding the mechanisms regulating both necrosis and apoptosis in cells is essential to being able to treat conditions, such as neurodegenerative diseases, stroke, coronary heart disease, kidney disease, and liver disease. A thorough understanding of necrotic and apoptotic cell death pathways is also crucial to treating AIDS and the conditions associated with AIDS, such as retinal necrosis.

Cell death has traditionally been categorized as either apoptotic or necrotic based on morphological characteristics (Wyllie et al., *Int. Rev. Cytol.* 68: 251 (1980)). These two modes of cell death were also initially thought to occur via regulated (caspase-dependent) and non-regulated processes,

respectively. More recent studies, however, demonstrate that the underlying cell death mechanisms resulting in these two phenotypes are much more complicated and, under some circumstances, interrelated. Furthermore, conditions that lead to necrosis can occur by either regulated caspase-independent or non-regulated processes.

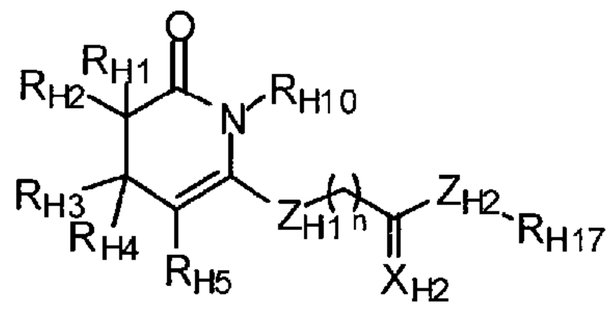
One regulated caspase-independent cell death pathway with morphological features resembling necrosis, called necroptosis, has recently been described (Degterev et al., *Nat. Chem. Biol.* 1:112 (2005)). This manner of cell death can be initiated with various stimuli (e.g., TNF-α and Fas ligand) and in an array of cell types (e.g., monocytes, fibroblasts, lymphocytes, macrophages, epithelial cells and neurons). Necroptosis may represent a significant contributor to and, in some cases, predominant mode of cellular demise under pathological conditions involving excessive cell stress, rapid energy loss, and massive oxidative species generation, where the highly energy-dependent apoptosis process is not operative.

The identification and optimization of low molecular weight molecules capable of inhibiting necroptosis will assist in elucidating its role in disease pathophysiology and could provide compounds (i.e., necrostatins) for anti-necroptosis therapeutics. The discovery of compounds that prevent caspase-independent cell death (e.g., necrosis or necroptosis) would also provide useful therapeutic agents for treating or preventing conditions in which necrosis occurs. These compounds and methods would be particularly useful for the treatment of neurodegenerative diseases, ischemic brain and heart injuries, and head trauma.

Summary of the Invention

The invention features a series of heterocyclic derivatives that inhibit tumor necrosis factor alpha (TNF-α) induced necroptosis. The invention further features pharmaceutical compositions featuring necrostatins. The compounds and compositions of the invention may also be used to treat disorders where necroptosis is likely to play a substantial role.

In a first aspect, the invention features a compound having a structure according to the following formula:



(I-A), where

each R_{H1}, R_{H2}, R_{H3}, R_{H4}, R_{H5}, R_{H10}, R_{H17}, X_{H2}, Z_{H1}, Z_{H2}, and n is as defined for Formula (I),

X_{H2} is selected, independently, from O, S, or NR_{H9};

each R_{H1}, R_{H2}, R_{H3}, R_{H4}, and R_{H5} is selected, independently from H, halogen, cyano, nitro, azido, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(=O)R_{H12}$, $-C(=O)OR_{H12}$, $-C(=O)NR_{H12}R_{H13}$, $-C(=S)R_{H12}$, $-C(=S)NR_{H12}R_{H13}$, $-C(=NR_{H14})R_{H12}$, $-C(=NR_{H14})NR_{H12}R_{H13}$, or $-[Z_{H1}-(CR_{H15}R_{H16})_n-\{C(=X_{H2})\}_o-Z_{H2}-R_{17}]$, or R_{H1} and R_{H3} combine to form a carbon-carbon double bond;

each Z_{H1} and Z_{H2} is selected, independently, from a single bond, O, S, or NR_{H11};

each R_{H9}, R_{H10}, R_{H11}, R_{H12}, R_{H13}, R_{H14}, R_{H15}, R_{H16}, and R_{H17}, is selected, independently from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

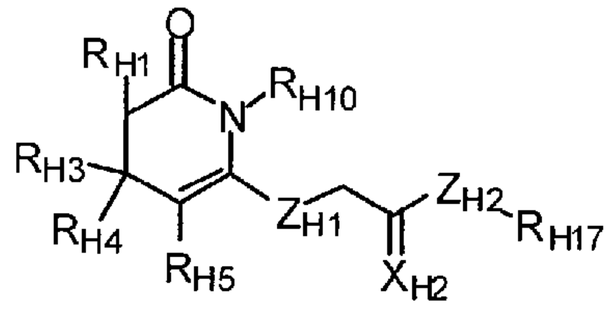
n is an integer between 0-6; and

o is 0 or 1; and

when R_{H1} is H, R_{H2} is H or CO_2Me, R_{H3} is H, R_{H4} is unsubstituted phenyl or phenyl substituted with 1, 2, or 3 substituents selected from methoxy, chloro, or fluoro, R_{H5} is CN, R_{H10} is H, Z_{H1} is S, n is 1, X_{H2} is O, and Z_{H2} is NH, R_{H17} is not H, methyl, methoxy, unsubstituted 2-thiazolyl, unsubstituted phenyl, 4-methoxyphenyl, 4-methylphenyl, 2-ethoxyphenyl, 4-isopropylphenyl, 4-fluorophenyl, or 2,4,6-trimethylphenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, the compound has a structure according to Formula (I-B)



(I-B), where

each R_{H1} and R_{H3} is selected, independently, from H, halogen, cyano, nitro, azido, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(=O)R_{H12}$, $-C(=O)OR_{H12}$, or $-C(=O)NR_{H12}R_{H13}$, or R_{H1} and R_{H3} combine to form a carbon-carbon double bond;

each R_{H4} and R_{H17} is selected, independently, from optionally substituted aryl or optionally substituted heteroaryl;

R_{H5} is selected from II, CN, $-C(=O)OR_{H12}$, or $-C(=O)NR_{H12}R_{H13}$;

each R_{H10}, R_{H11}, R_{H12}, and R_{H13} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

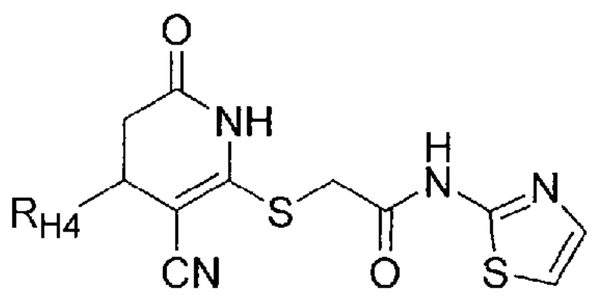
Z_{H1} is selected from a single bond or S;

Z_{H2} is selected from a single bond or NR_{H11}; and

X_{H2} is O or S;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In other embodiments, the compound has the following structure:



(I-C),

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{H1} and R_{H3} are H.

In some embodiments, R_{H5} is CN.

In some embodiments, R_{H10} is H.

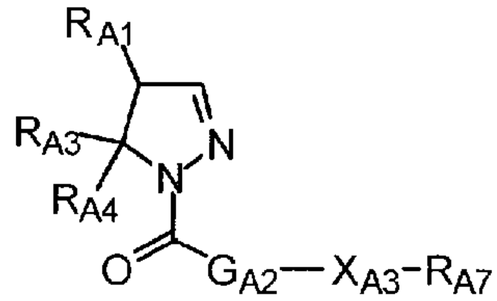
In some embodiments, Z_{H1} is S.

In some embodiments, Z_{H2} is NH,

In some embodiments, R_{H4} is unsubstituted phenyl or phenyl having 1, 2, 3, 4, or 5 substituents. In further embodiments, the phenyl includes 1, 2, or 3 substituents selected from F, Cl, or OR_{H18}, where each R_{H18} is, independently, selected from H or optionally substituted C_{1-6} alkyl. In certain embodiments, the phenyl is 2-fluorophenyl, 2-chlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3, 4, 5-trimethoxyphenyl, or 3, 4-dimethoxyphenyl.

In some embodiments, R_{H17} is optionally substituted heteroaryl. In certain embodiments, heteroaryl selected from furan, thiophene, pyrrole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,3-oxadiazole or 1,2,5-oxadiazole, oxazole, benzoxazole, isoxazole, isothiazole, pyrazole, thiazole, benzthiazole, 1,2,4-triazole, 1,2,3-triazole, benzotriazole, pyridine, pyrimidine, pyrazines, quinoline, isoquinoline, purine, pyrazine, pteridine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, indole, 1,2,4,5-tetrazine, benzo[*b*]thiophene, benzo[*c*]thiophene, benzofuran, isobenzofuran, and benzimidazole.

In a second aspect, the invention features a compound having a structure according to the following formula



(II-A), where

each R_{A1}, R_{A3}, and R_{A4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

G_{A2} is absent or $-(CR_{A11}R_{A12})_n-$;

X_{A3} is absent or is O, S, or NR_{A8};

each R_{A8} and R_{A13} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-COR_{A14}$, $-CO_2R_{A14}$, or $-CONR_{A14}R_{A15}$;

each R_{A9}, R_{A10}, R_{A11}, and R_{A12} is selected, independently, from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{A7}, R_{A14} and R_{A15} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl; and

each m and n is, independently, 1, 2, or 3; and

where when one of R_{A1} and R_{A4} is H and the other is selected from H or CO_2Et, and R_{A3} is unsubstituted phenyl, G_{A2}-X_{A3}-R_{A7} is not NHC_6H_5, NH(p-C_6H_4F), NH(p-C_6H_4OH), NH(p-C_6H_4OMe), NH(3-OH-4-Cl-C_6H_4), $-CH_2$(O-*p*-C_6H_4Me), $-CH_2$(4-ethylpiperazinyl), $-CH_2S$(2-phenyltetrazolyl), $-CH_2S$(4-chlorophenyl), $-CH_2S$(2-benzothiazolyl), $-CH_2S$(2-(N-methylimidazolyl)), $-CH_2S$(4,6-dimethylquinazolinyl), adamantyl, or optionally substituted oxiranyl; and

where when R_{A1} and R_{A4} are each H and R_{A3} is 4-methoxyphenyl, G_{A2}-X_{A3}-R_{A7} is not optionally substituted oxiranyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{A1} and R_{A4} are H.

In some embodiments, R_{A3} is unsubstituted phenyl.

In some embodiments, R_{A3} is phenyl having 1, 2, 3, 4, or 5 substituents.

In some embodiments, G_{A2} is absent.

In certain embodiments, X_{A3} is absent and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

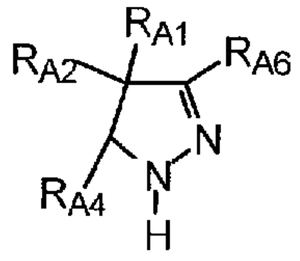
In other embodiments, X_{A3} is NR_{A8} and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In some embodiments, G_{A2} is CH_2.

In some embodiments, X_{A3} is S and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In some embodiments, X_{A3} is absent and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In a third aspect, the invention features compounds according to the following formula



(II-C), where

each R_{A1}, R_{A2}, R_{A4}, and R_{A6} is selected, independently, from H, -C(=O)-X_{A3}-R_{A7}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

each X_{A3} is, independently, absent, -O-, or -NR_{A8}-,

each R_{A8} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -COR_{A14}, -CO_2R_{A14}, or -$CONR_{A14}R_{A15}$;

each R_{A7}, R_{A14} and R_{A15} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl; and

wherein when R_{A1} and R_{A4} combine to form a carbon-carbon double bond and R_{A2} is H, R_{A6} is not 4-chlorophenyl, 4-methoxyphenyl, or 4-($NHCO_2{}^tBu$)phenyl; and

where when R_{A1} is H, R_{A4} is H or CO_2Et, R_{A2} is unsubstituted phenyl, R_{A6} is not –C(=O)-(unsubstituted phenyl) or –C(=O)-(4-methylphenyl); and

where when R_{A1} is H, R_{A4} is –C(=O)-(unsubstituted phenyl), R_{A2} is 4-chlorophenyl, R_{A6} is not CO_2Et;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{A5} is H; each R_{A1}, R_{A2}, R_{A4}, and R_{A6} is selected, independently, from H, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)-X_{A3}-R_{A7}, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond; each R_{A7} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each X_{A3} is, independently, absent, -O-, or -NR_{A8}-,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In certain embodiments, R_{A1} and R_{A4} combine to form a carbon-carbon double bond.

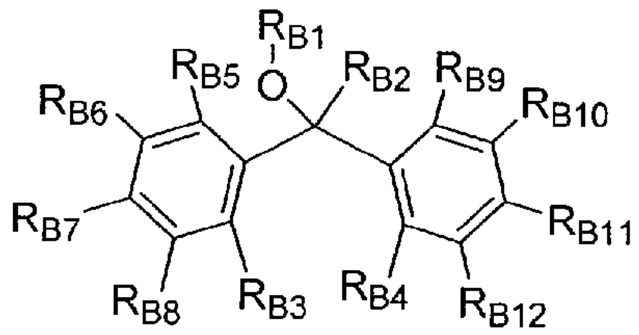
In other embodiments, R_{A6} is optionally substituted aryl or optionally substituted heteroaryl.

In some embodiments, R_{A6} is a phenyl group having a substituent at the 4-position.

In certain embodiments, R_{A1} and R_{A4} are each H, R_{A2} is optionally substituted aryl or optionally substituted heteroaryl, and R_{A6} is $-C(=O)-X_{A3}-R_{A7}$.

In other embodiments, R_{A2} is unsubstituted phenyl.

In a fourth aspect, the invention features a compound having a structure according to the following formula:



(III), where

R_{B1} is selected from H, optionally substituted C_{1-6} alkyl, $-C(=O)R_{B18}$, $-C(=O)OR_{B18}$, or $-C(=O)NR_{B18}R_{B19}$;

R_{B2} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R_{B3} and R_{B4} is selected, independently from H, optionally substituted C_{1-6} alkyl, or R_{B3} and R_{B4} combine to form a bridging group having the structure $-(CH_2)_n-(CR_{B13}=CR_{B14})_o-(CH_2)_p-$;

each n, o, and p is, independently, 0 or 1;

each R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H, halogen, –CN, $-NO_2$, $-N_3$, $-R_{B13}$, $-OR_{B13}$, $-SR_{B13}$, $-NR_{B13}R_{B14}$, $-C(=O)R_{B15}$, $-C(=O)OR_{B15}$, $-C(=O)NR_{B15}R_{B16}$, $-OC(=O)R_{B15}$, $-OC(=O)OR_{B15}$, $-OC(=O)NR_{B15}R_{B16}$, $-NR_{B15}C(=O)R_{B15}$, $-NR_{B15}C(=O)OR_{B16}$, $-NR_{B15}C(=O)NR_{B16}R_{B17}$, $-C(=S)R_{B15}$, $-C(=S)NR_{B15}R_{B16}$, $-NR_{B15}C(=S)R_{B16}$, $-NR_{B15}C(=S)NR_{B16}R_{B17}$, $-C(=NR_{B13})NR_{B15}R_{B16}$, $-NR_{B15}C(=NR_{B13})R_{B16}$, $-NR_{B15}C(=NR_{B13})NR_{B16}R_{B17}$;

each R_{B13} and R_{B14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R_{B18}$, $-C(=O)OR_{B18}$, or $-C(=O)NR_{B18}R_{B19}$,

each R_{B15}, R_{B16}, R_{B17}, R_{B18}, and R_{B19} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

where when each n, o, and p is 0, R_{B3} and R_{B4} combine to form a single bond, and

where R_{B1} is not H or CH_3 when R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B9}, R_{B10}, R_{B11}, and R_{B12} are each H, R_{B2} is ethyl, ethenyl, 2-haloethenyl, ethynyl, haloethynyl, propynyl, or -C≡C-C(OH)$(CH_3)_2$, and when R_{B3} and R_{B4} are each H or combine to form a bond, $–CH_2CH_2-$ or –CH=CH-;

where R_{B1} is not H when R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B10}, and R_{B11} are each H, at least one of R_{B9} or R_{B12} is fluoro, R_{B2} is ethynyl, and when R_{B3} and R_{B4} combine to form $–CH_2CH_2-$;

wherein R_{B1} is not H when R_{B5}, R_{B7}, R_{B9}, and R_{B11} are H and one or two of R_{B6}, R_{B8}, R_{B10}, and R_{B12} is halogen, nitro, or methyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{B1} is H.

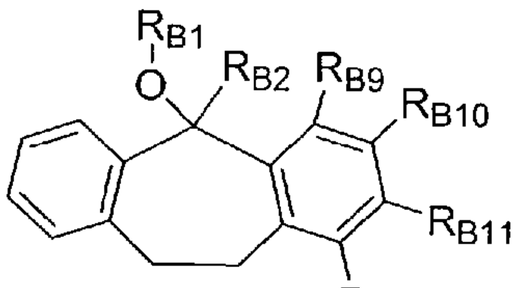
In some embodiments, R_{B2} is C_{1-3} alkyl.

In certain embodiments, R_{B2} is C_{1-3} alkenyl.

In other embodiments, R_{B2} is ethynyl.

In some embodiments, R_{B3} and R_{B4} are each H.

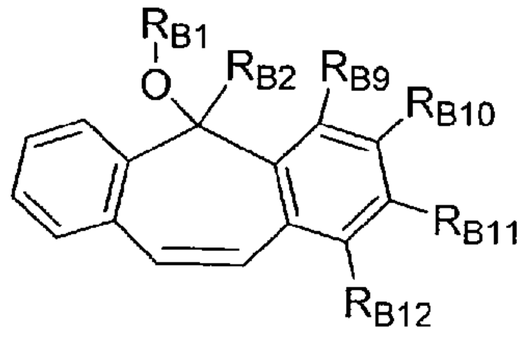
In certain embodiments, the compound has the following structure



(III-A), where

R_{B2} is ethyl, ethenyl, or ethynyl and each R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from II and halogen, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof. In some embodiments, R_{B10} or R_{B12} is fluoro.

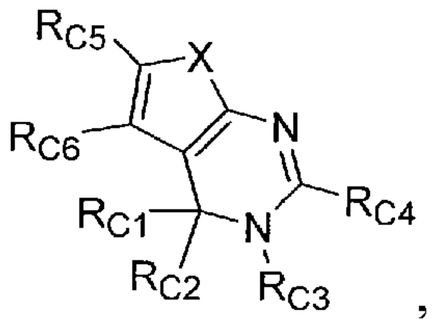
In some embodiments, the compound has the following structure:



(III-B), where

R_{B2} is ethyl, ethenyl, or ethynyl and each R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H and halogen, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In a fifth aspect, the invention features a structure according to the following formula



, where

each R_{C1}, R_{C2}, and R_{C3} is selected, independently, from H, optionally substituted C_{1-6} alkyl, -Y-R_{C7}, or R_{C1} and R_{C2} combine to form a (=O) or a (=S) group, or R_{C1} and R_{C3} combine to form a carbon-nitrogen double bond;

R_{C4} is selected from H, halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or -C(=O)ZR_{C8},

each R_{C5} and R_{C6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, or R_{C5} and R_{C6} combine to form an optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{C7}, R_{C8}, R_{C9}, R_{C10}, R_{C11}, and R_{C12} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

X is –CR_{C11}=CR_{C12}-, O, S, or NR_{C9};

Y is, independently, a single bond, $(CR_{C8}R_{C9})_n$, O, S, or NR_{C10}; and

Z is a single bond, O, S, or NR_{C10};

n is an integer between 0-4; and

where when X is S, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} combine to form unsubstituted cyclopentyl, R_{C3} is not $-CH_2-R_{C7}$, where R_{C7} is unsubstituted phenyl, unsubstituted naphthyl, unsubstituted 8-quinolyl, unsubstituted 2-oxoquinolyl, or phenyl having 1 or 2 substituents selected from F, OMe, Me, CN, or Cl; and

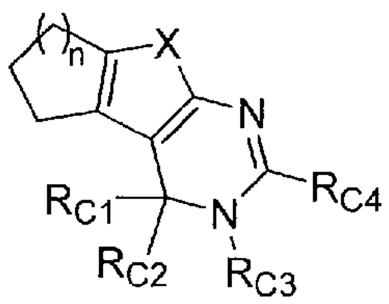
wherein when X is S, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} are each CH_3, R_{C3} is not $-CH_2-R_{C7}$, where R_{C7} is unsubstituted phenyl; and

where when X is CH=CH, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} are H, R_{C3} is not $-CH_2$(4-halophenyl);

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, each R_{C5} and R_{C6} is optionally substituted C_{1-6} alkyl.

In other embodiments, the compound has a structure according to the following formula:



(IV-A), wherein X, R_{C1}, R_{C2}, R_{C3}, and R_{C4} are as defined for Formula (IV) and n is an integer between 0-3,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{C1} and R_{C2} combine to form a (=O) group.

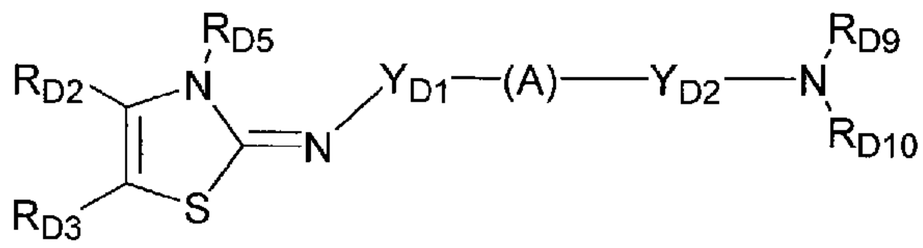
In other embodiments, X is S.

In some embodiments, n is 1.

In certain embodiments, R_{C3} is $-Y-R_{C7}$.

In other embodiments, R_{C3} is $-(CH_2)$-(optionally substituted aryl).

In a sixth aspect, the invention features a compound having a structure according to the following formula



(V-A), where

each Y_{D1} and Y_{D2} is selected, independently, from -C(=O)- or -S(=O)$_2$-;

A is phenyl having 0, 1, 2, 3, or 4 additional substituents;

R_{D2} and R_{D3} are selected, independently from H, halogen, CN, NC, N_3, NO_2, -COR_{D13}, -CO_2R_{D13}, -$CONR_{D13}R_{D14}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{D5}, R_{D9}, R_{D10}, R_{D13}, and R_{D14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{D9} and R_{D10} combine to form a heterocyclyl; and

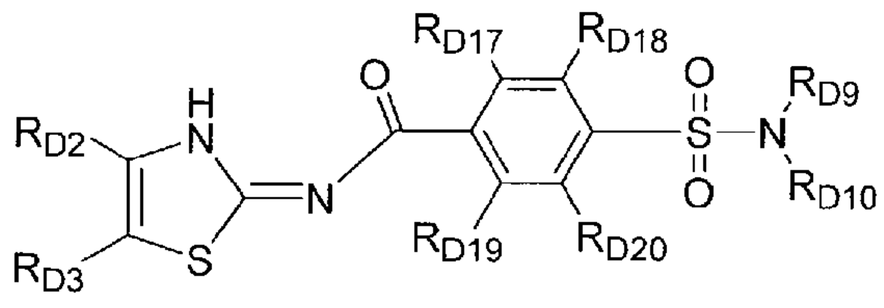
where when R_{D2}, R_{D3}, and R_{D5} are H, Y_{D1} is –(C=O)-, Y_{D2} is –(SO_2)-, and R_{D9} and R_{D10} are each ethyl or R_{D9} is methyl and R_{D10} is CH_2(2-tetrahydrofuran), and A is phenyl having 0 additional substituents, Y_{D1} and Y_{D2} are not para to each other,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, Y_{D1} and Y_{D2} are *ortho* or *meta* to each other.

In other embodiments, Y_{D1} and Y_{D2} are *para* to each other.

In some embodiments, the compound has a structure according to the following formula



(V-B), where

each R_{D2}, R_{D3}, R_{D17}, R_{D18}, R_{D19}, and R_{D20}, is selected, independently from H, halogen, CN, NC, N_3, NO_2, -COR_{D13}, -CO_2R_{D13}, -$CONR_{D13}R_{D14}$,

optionally substituted C_{1-6} alkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R_{D9} and R_{D10} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, or optionally substituted aryl, or R_{D9} and R_{D10} combine to form a heterocyclyl;

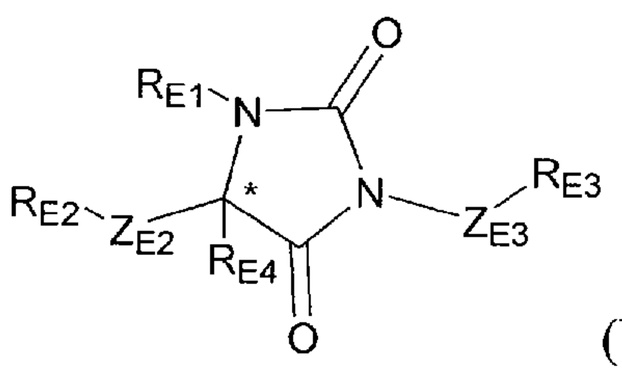
or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{D17}, R_{D18}, R_{D19}, and R_{D20} are H.

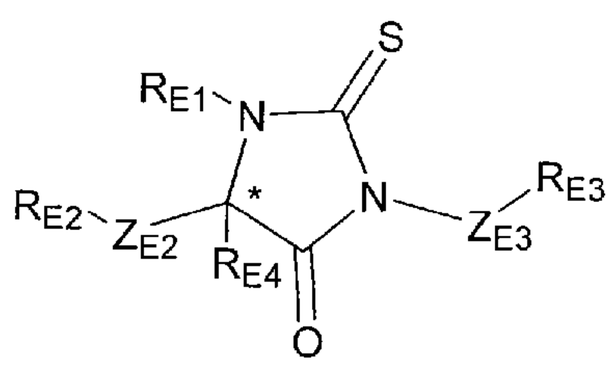
In some embodiments, R_{D2} and R_{D3} are H.

In other embodiments, R_{D9} and R_{D10} are each optionally substituted C_{1-6} alkyl.

In a seventh aspect, the invention features a compound having a structure according to



(VI-A) or



(VI-B),

where

each Z_{E2} and Z_{E3} is selected, independently, from a single bond, $-(CR_{E6}R_{E7})_n-$, -C(=O)-, or R_{E1} and Z_{E2}-R_{E2} combine to form a double bond;

each R_{E1}, R_{E2}, and R_{E4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R_{E3} is selected from optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

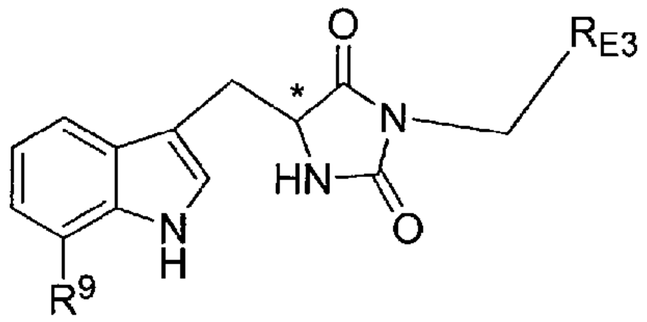
each R_{E6} and R_{E7} is selected, independently, from H or optionally substituted C_{1-6} alkyl; and

each n is an integer between 1-6; and

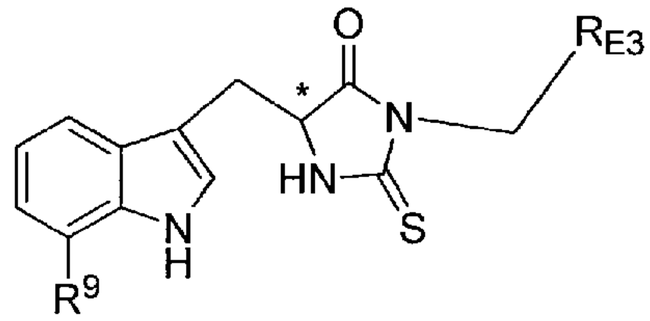
where when R_{E1} and R_{E4} are H, Z_{E2} and Z_{E3} are each CH_2, and R_{E2} is unsubstituted 3-indolyl, R_{E3} is not 4-chlorophenyl or $CH_2CH_2O(p\text{-}C_6H_4F)$,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, the compound has a structure according to



(VI-D-3) or



(VI-D-4), where

R_{E3} is optionally substituted aryl or optionally substituted heteroaryl; and

R^9 is H, halogen, CN, NO_2, OR^{13}, $NR^{13}R^{14}$, COR^{15}, CO_2R^{15}, or optionally substituted $C_{1\text{-}6}$ alkyl;

each R^{13} and R^{14} is selected, independently, from H, COR^{16}, CO_2R^{16}, optionally substituted $C_{1\text{-}6}$ alkyl, optionally substituted $C_{3\text{-}10}$ cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and,

each R^{15} and R^{16} is selected, independently, from H, optionally substituted $C_{1\text{-}6}$ alkyl, optionally substituted $C_{3\text{-}10}$ cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{E3} is optionally substituted aryl.

In some embodiments, R_{E3} is unsubstituted $C_{3\text{-}10}$ cycloalkyl, unsubstituted heterocyclyl, unsubstituted aryl, or unsubstituted heteroaryl.

In other embodiments, R_{E3} is substituted $C_{3\text{-}10}$ cycloalkyl, substituted heterocyclyl, substituted aryl, or substituted heteroaryl. In other embodiments, the substituted $C_{3\text{-}10}$ cycloalkyl, substituted heterocyclyl, substituted aryl, or substituted heteroaryl includes 1, 2, 3, 4, or 5 substituents selected,

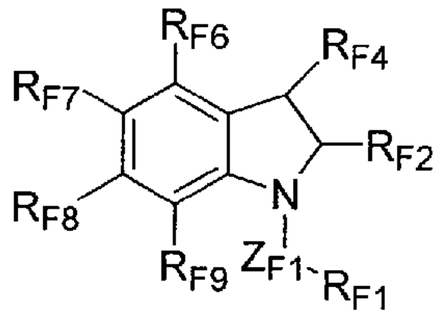
independently, from the group consisting of: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, $-N_3$, -OR', -NR'C(=O)R", –C(=O)NRR', -NRR', -OC(=O)NR'R", -NRC(=O)OR', -OH, and -NC), wherein each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

In still other embodiments, R_{E3} is substituted aryl or substituted heteroaryl. In some embodiments, R_{E3} is substituted phenyl. In some embodiments, the substituted phenyl is substituted with at least one halogen. In other embodiments, the substituted phenyl is substituted with 1, 2, 3, 4, or 5 substituents selected, independently, from the group consisting of: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, $-N_3$, -OR', -NR'C(=O)R", –C(=O)NRR', -NRR', -OC(=O)NR'R", -NRC(=O)OR', -OH, and -NC), wherein each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

In some embodiments, the stereocenter marked by the asterisk in the compound of Formula (VI) has the (*R*)-configuration. In other embodiments, the stereocenter marked by the asterisk has the (*S*)-configuration.

In any of the embodiments described herein, one or both of $-Z_{E3}$ and R_{E3} does not include substituents selected from the group consisting of: halogen (e.g., F, Cl, Br, or I); nitro ($-NO_2$), cyano (-CN), acyloxy(-OC(=O)R'), acyl (-C(=O)R'), carboxylic acid ($-CO_2H$), carboxylic ester ($-CO_2R'$), sulfonate ($-S(=O)_2OR$), sulfonamide ($-S(=O)_2NRR'$ or $–NRS(=O)_2R'$), or sulfonyl ($-S(=O)_2R$), where each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, as described herein.

In an eighth aspect, the invention features a compound having a structure according to the following formula,



(VII-A), where

Z_{F1} is selected from a single bond, -(CH_2)-, -C(=O)-, or -S(=O)$_2$-;

R_{F1} is selected from H, OR_{F14}, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R_{F2} and R_{F4} are each H, or R_{F2} and R_{F4} combine to form a carbon-carbon double bond;

each R_{F6}, R_{F7}, R_{F8}, and R_{F9} is selected, indcpendently, from H, halogen, CN, NC, N_3, NO_2, OR_{F12}, SR_{F12}, $NR_{F12}R_{F13}$, -COR_{F12}, -$CO_{2\,F12}$, -$CONR_{F12}R_{F13}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R_{F12}, R_{F13}, and R_{F14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

where when R_{F2}, R_{F4}, R_{F6}, R_{F7}, R_{F8}, and R_{F9} are each H and Z_{F1} is -C(=O)-, R_{F1} is not -(unsubstituted 1,4-benzodioxane) or -CH_2-O-(unsubstituted phenyl), or -CH(CH_3)O(*o*-tolyl);

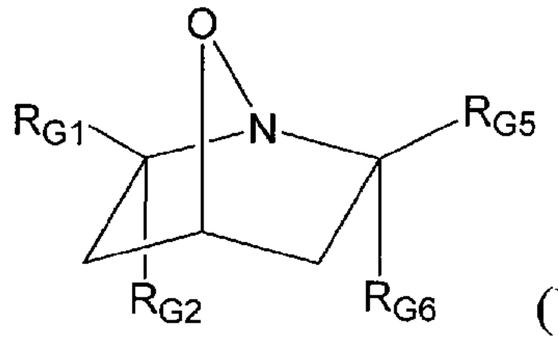
or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{F2} and R_{F4} are each H.

In other embodiments, R_{F6}, R_{F7}, R_{F8}, and R_{F9} are H.

In certain embodiments, Z_{F1} is -C(=O)-. In further embodiments, R_{F1} is optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In a ninth aspect, the invention features a compound having a structure according to the following formula



(VIII-A), where

each R_{G1}, R_{G2}, R_{G5}, and R_{G6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{G1} and R_{G2}, or R_{G5} and R_{G6} combine to form an optionally substituted cycloalkyl or heterocyclyl; and

where when R_{G1} is unsubstituted phenyl and R_{G2} is H, R_{G5} and R_{G6} do not combine to form unsubstituted cyclopentyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{G1} or R_{G5} is phenyl having 0, 1, 2, 3, 4, or 5 substituents. In certain embodiments, R_{G1} is unsubstituted phenyl.

In some embodiments, R_{G2} or R_{G6} is phenyl having 0, 1, 2, 3, 4, or 5 substituents.

In other embodiments, R_{G1} and R_{G2}, or R_{G5} and R_{G6} combine to form an optionally substituted cycloalkyl. In certain embodiments, the cycloalkyl is cyclopropyl, cyclobutyl ,cyclopentyl, or cyclohexyl.

In a tenth aspect, the invention features a pharmaceutical composition including a pharmaceutically acceptable excipient and any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70), or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

In an eleventh aspect, the invention features a method of treating a condition in a subject, with the method including the step of administering the compound of any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70), or any pharmaceutically

acceptable salt or solvate thereof, or stereoisomer thereof, to said subject in a dosage sufficient to decrease necroptosis.

In some embodiments, the condition is a neurodegenerative disease of the central or peripheral nervous system, the result of retinal neuronal cell death, the result of cell death of cardiac muscle, the result of cell death of cells of the immune system; stroke, liver disease, pancreatic disease, the result of cell death associated with renal failure; heart, mesenteric, retinal, hepatic or brain ischemic injury, ischemic injury during organ storage, head trauma, septic shock, coronary heart disease, cardiomyopathy, myocardial infarction, bone avascular necrosis, sickle cell disease, muscle wasting, gastrointestinal disease, tuberculosis, diabetes, alteration of blood vessels, muscular dystrophy, graft-versus-host disease, viral infection, Crohn's disease, ulcerative colitis, asthma, or any condition in which alteration in cell proliferation, differentiation or intracellular signaling is a causative factor.

In some embodiments, the condition is a neurodegenerative disease of the central or peripheral nervous system.

In some embodiments, the condition is hepatic or brain ischemic injury, or ischemic injury during organ storage, head trauma, septic shock, or coronary heart disease.

In some embodiments, the condition is stroke.

In some embodiments, the condition is myocardial infarction.

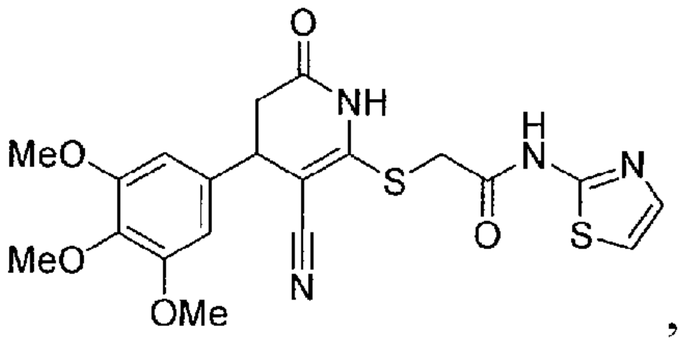
In a twelfth aspect, the invention features a method of decreasing necroptosis, where the method includes contacting a cell with any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70)), or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

In a thirteenth aspect, the invention features a kit including

(a) a pharmaceutical composition comprising any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70), or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof; and

(b) instructions for the use of the pharmaceutical composition of (a) to treat a condition in a subject.

In any of the compositions, methods, and kits of the invention, the compound can be selected from the group consisting of: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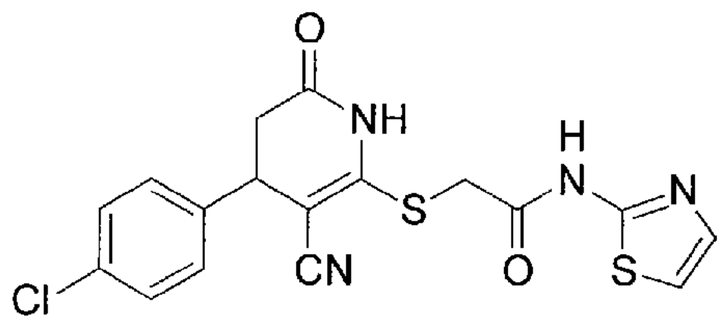
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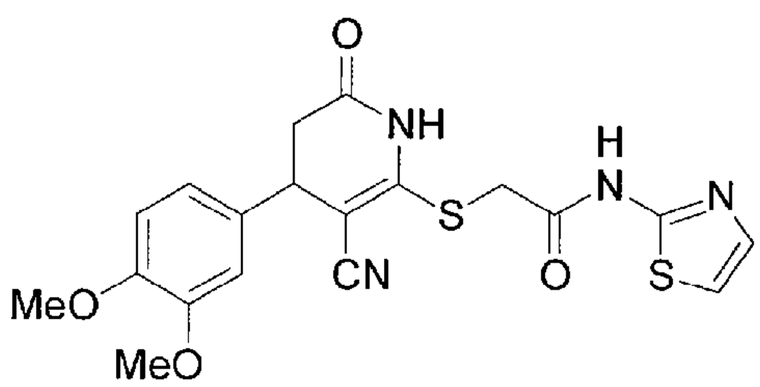
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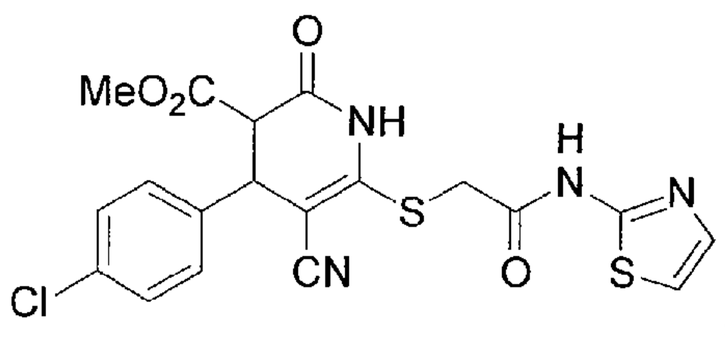
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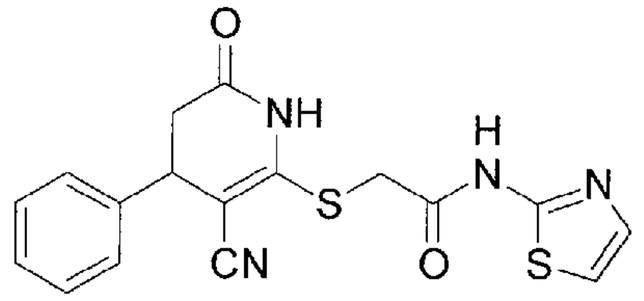
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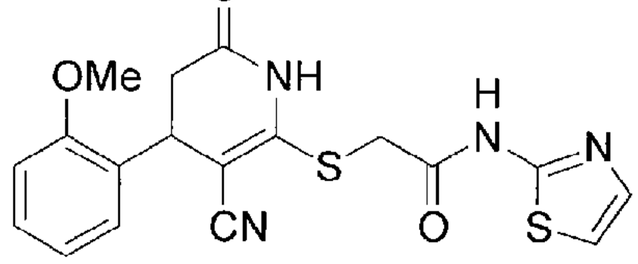
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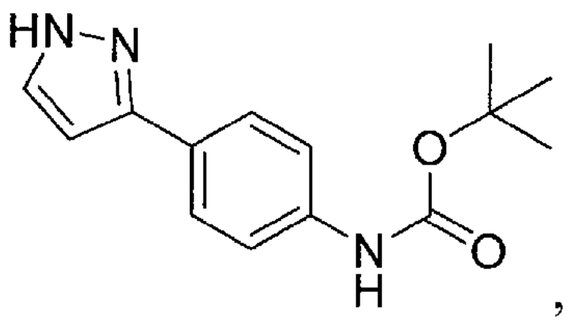
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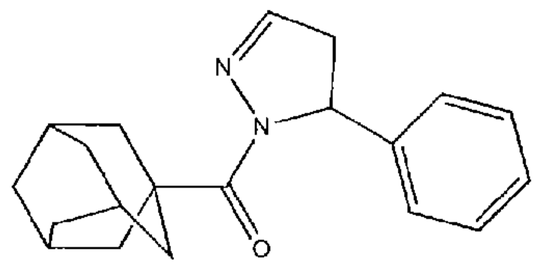
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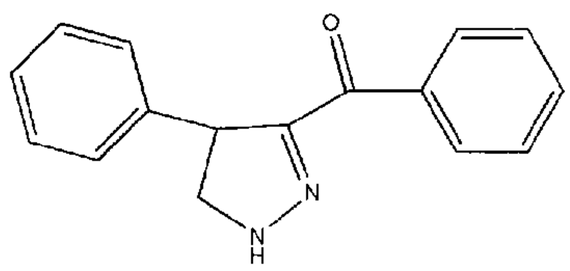
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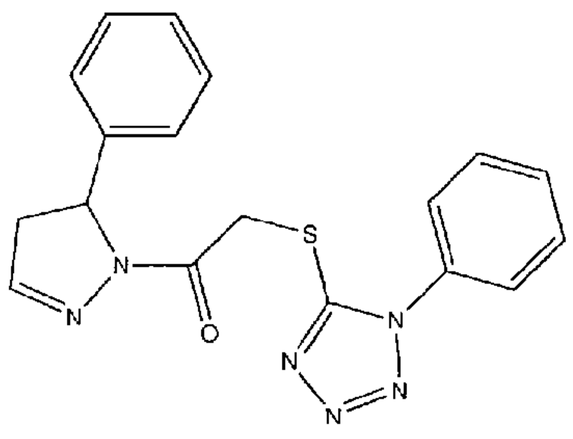
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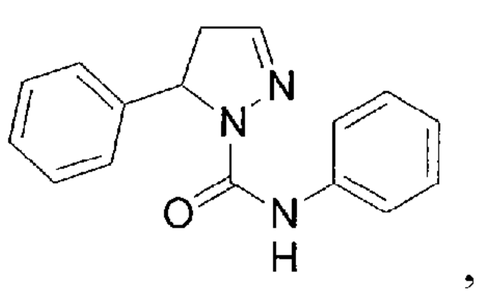
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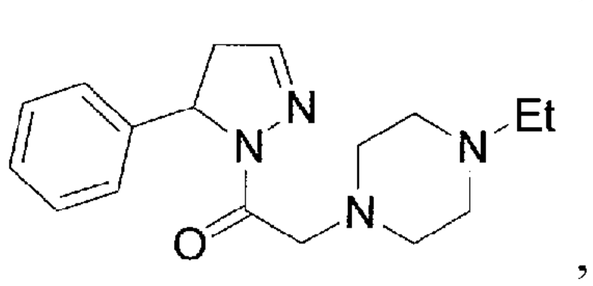
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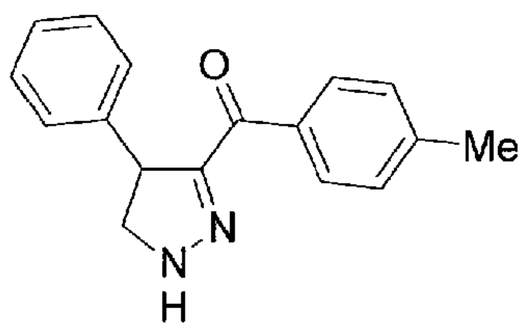
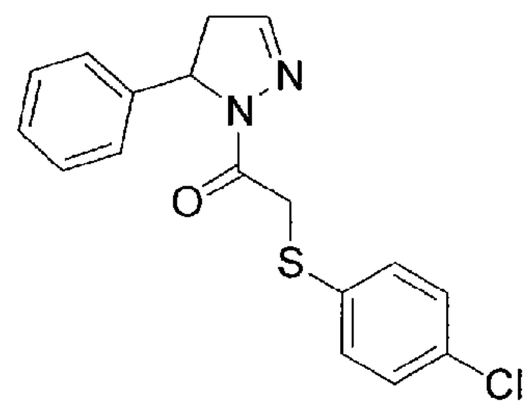
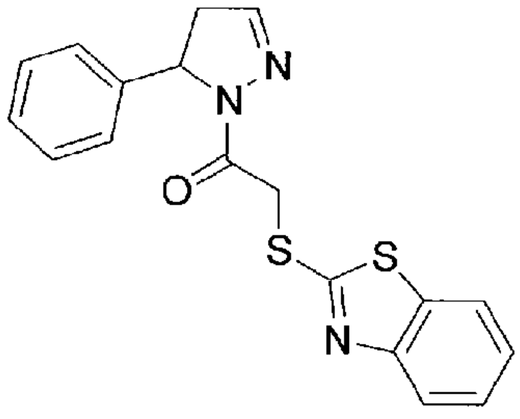
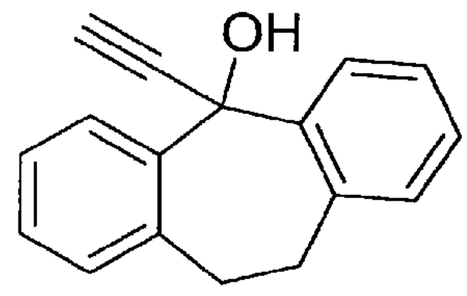
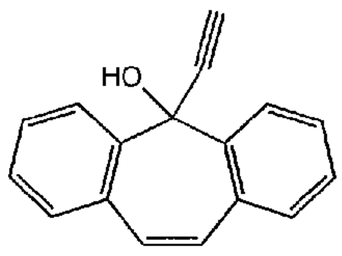
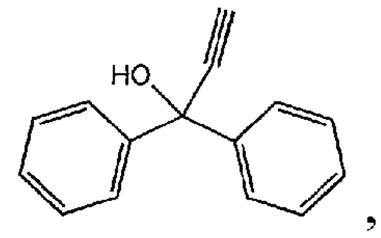
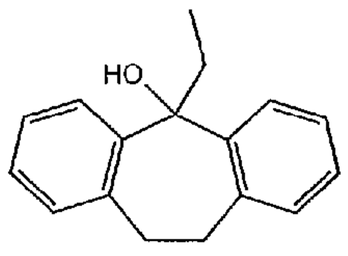
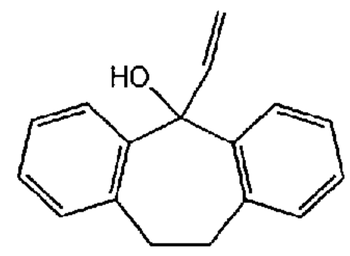
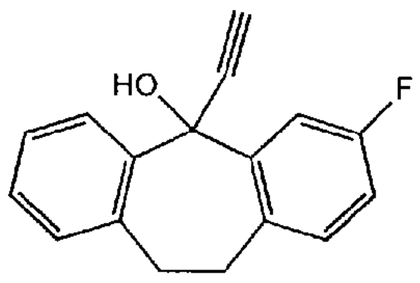
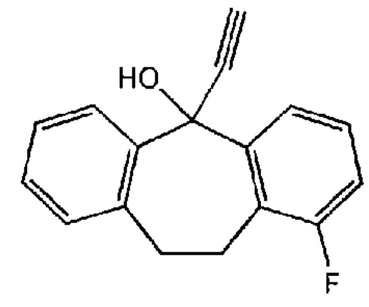
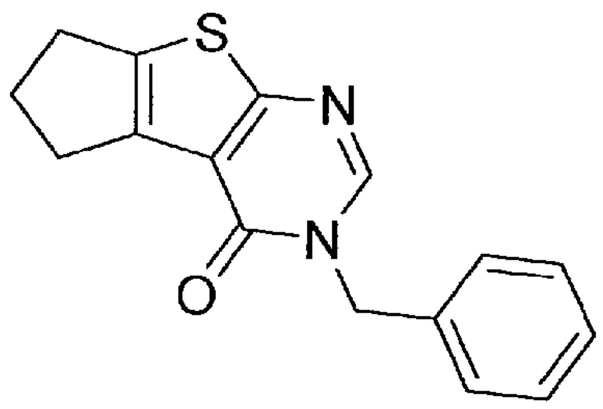
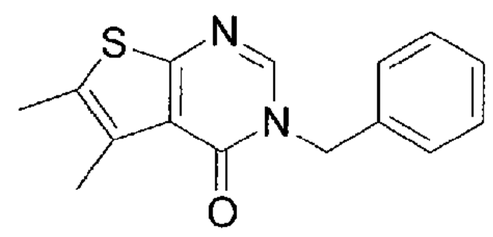
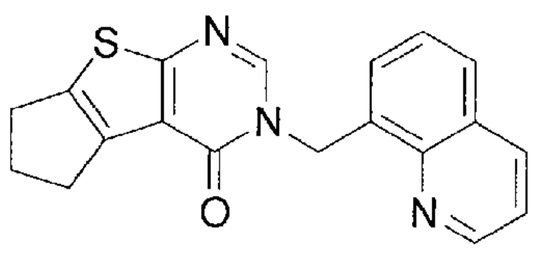
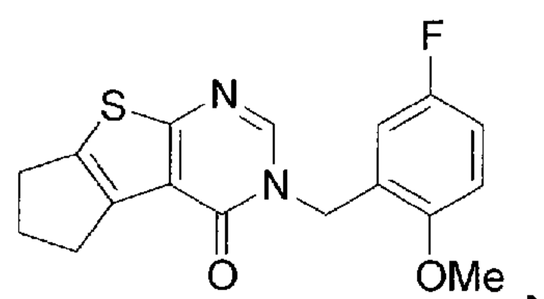
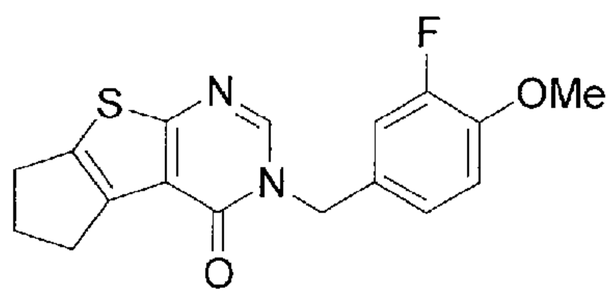
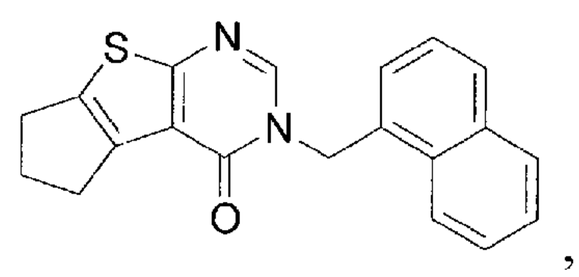

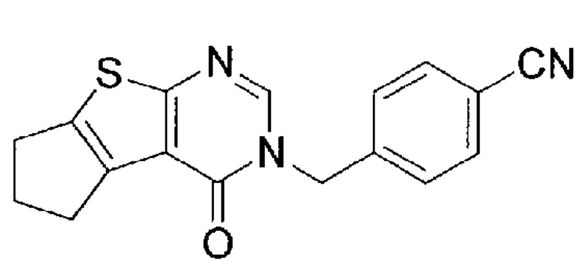
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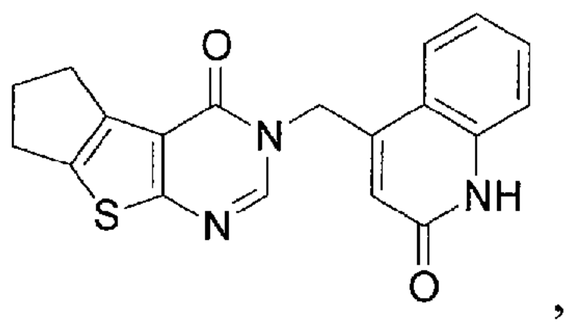
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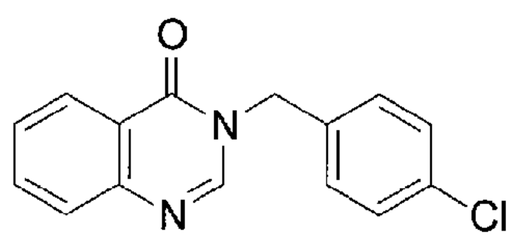
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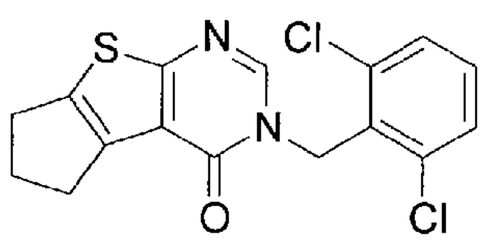
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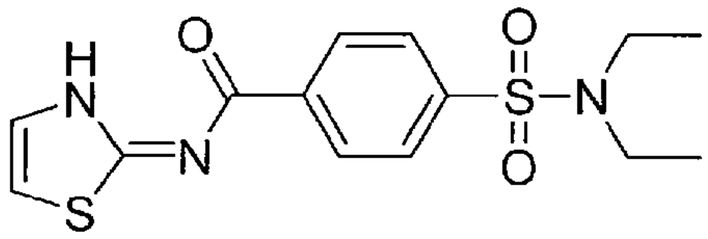
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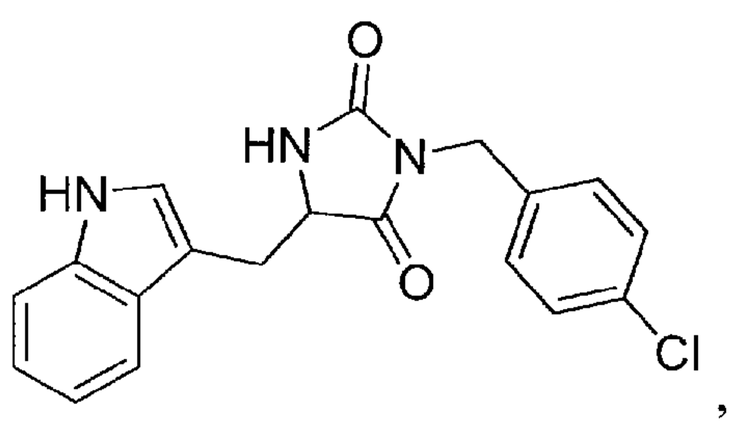
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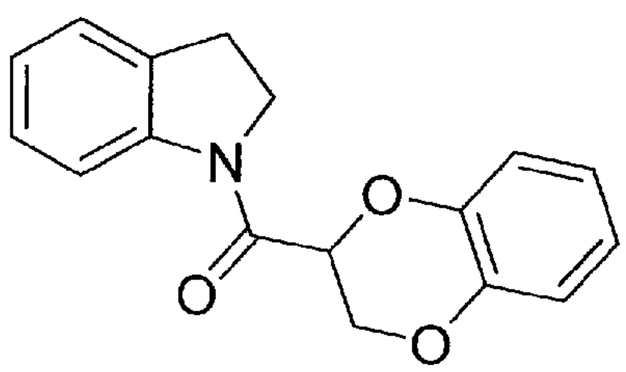
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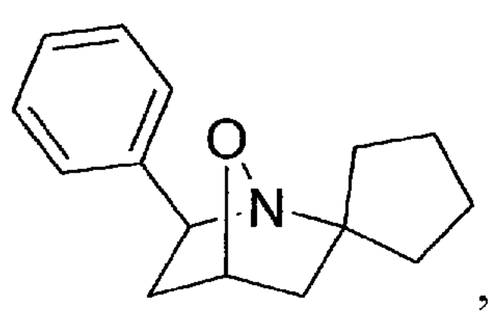
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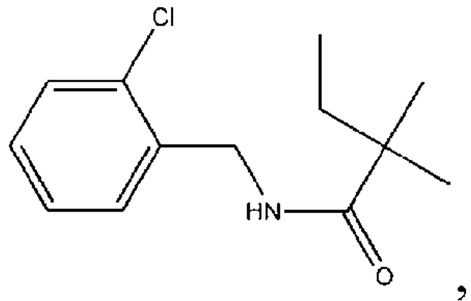
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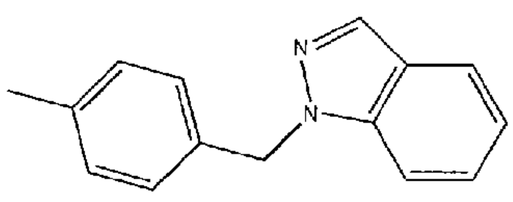
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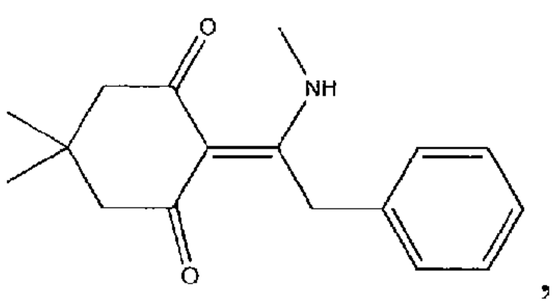
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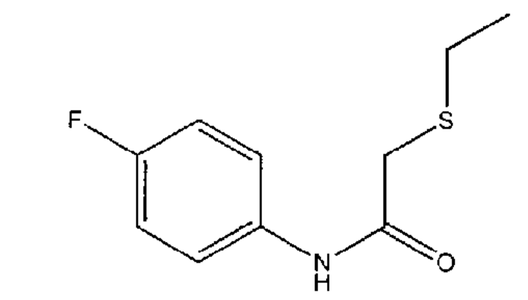
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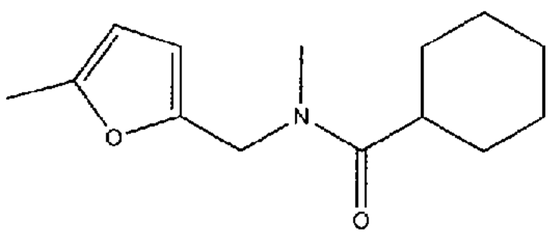
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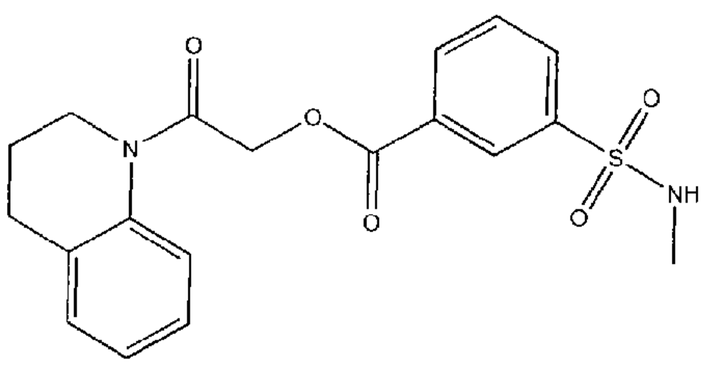
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or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

By "C_{1-4} alkaryl" is meant a C_{1-4} alkyl group having an optionally substituted aryl or an optionally substituted heteroaryl located at any position of the carbon chain. The C_{1-4} alkyl group may be linear or branched and may also be substituted with, for example, 1, 2, 3, 4, or 5 additional substituents as described herein.

By "alkoxy" is meant a group having the structure -O(optionally substituted C_{1-6} alkyl), where the optionally substituted C_{1-6} alkyl may be branched, linear, or cyclic. The C_{1-6} alkyl may be substituted or unsubstituted. A substituted C_{1-6} alkyl can have, for example, 1, 2, 3, 4, 5, or 6 substituents located at any position. Exemplary alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy, and the like.

By "C_{2-6} alkenyl" or "alkenyl" is meant an optionally substituted unsaturated C_{2-6} hydrocarbon group having one or more carbon-carbon double bonds. Exemplary C_{2-6} alkenyl groups include, but are not limited to -CH=CH (ethenyl), propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. A C_{2-6} alkenyl may be linear or branched and may be unsubstituted or substituted. A substituted C_{2-6} alkenyl may have, for example, 1, 2, 3, 4, 5, or 6 substituents located at any position.

By "C_{1-6} alkyl" or "alkyl" is meant an optionally substituted C_{1-6} saturated hydrocarbon group. An alkyl group may be linear, branched, or cyclic ("cycloalkyl"). Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n–propyl, isopropyl, n–butyl, iso–butyl, sec–butyl, sec–pentyl, iso–pentyl, tert–butyl, n–pentyl, neopentyl, n–hexyl, sec–hexyl, n–heptyl, n–octyl, n–decyl, n–undecyl, dodecyl, and the like, which may bear one or more sustitutents. Substituted alkyl groups may have, for example, 1, 2, 3, 4, 5, or 6 substitutents located at any position. Exemplary substituted alkyl groups include, but are not limited to, optionally substituted C_{1-4} alkaryl groups.

By "C_{2-6} alkynyl" or "alkynyl" is meant an optionally substituted unsaturated C_{2-6} hydrocarbon group having one or more carbon-carbon triple

bonds. Exemplary C_{2-6} alkynyl groups include, but are not limited to ethynyl, 1-propynyl, and the like

By "amino" is meant a group having a structure –NR'R", where each R' and R" is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or R' and R" combine to form an optionally substituted heterocyclyl. When R' is not H or R" is not H, R' and R" may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "aryl" is meant is an optionally substituted C_6-C_{14} cyclic group with $[4n + 2]$ π electrons in conjugation and where n is 1, 2, or 3. Non-limiting examples of aryls include heteroaryls and, for example, benzene, naphthalene, anthracene, and phenanthrene. Aryls also include bi– and tri–cyclic ring systems in which a non-aromatic saturated or partially unsaturated carbocyclic ring (e.g., a cycloalkyl or cycloalkenyl) is fused to an aromatic ring such as benzene or napthalene. Exemplary aryls fused to a non-aromatic ring include indanyl, tetrahydronaphthyl,. Any aryls as defined herein may be unsubstituted or substituted. A substituted aryl may be optionally substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents located at any position of the ring.

By "aryloxy" is meant a group having the structure -O(optionally substituted aryl), where aryl is as defined herein.

By "azido" is meant a group having the structure $–N_3$.

By "carbamate" or "carbamoyl" is meant a group having the structure -OCONR'R" or –NR'CO_2R", where each R' and R" is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or R' and R" combine to form an optionally substituted heterocyclyl. When R' is not H or R" is not H, R' and R" may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "carbonate" is meant a group having a the structure -OCO_2R', where R' is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted

cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. When R' is not H, R may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "carboxamido" or "amido" is meant a group having the structure -CONR'R" or -NR'C(=O)R", where each R' and R" is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or R' and R" combine to form an optionally substituted heterocyclyl. When R' is not H or R" is not H, R' and R" may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "carboxylic group" is meant a group having the structure $-CO_2R'$, where R' is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. When R' is not H, R may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "cyano" is meant a group having the structure –CN.

By "C_{3-10} cycloalkyl" or "cycloalkyl" is meant an optionally substituted, saturated or partially unsaturated 3– to 10–membered monocyclic or polycyclic (e.g., bicyclic, or tricyclic) hydrocarbon ring system. Where a cycloalkyl is polycyclic, the constituent cycloalkyl rings may be fused together, form a spirocyclic structure, or the polycyclic cycloalkyl may be a bridged cycloalkyl (e.g., adamantyl or norbonanyl) . Exemplary cycloalkyls incluce cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Cycloalkyls may be unsubstituted or substituted. A substituted cycloalkyl can have, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "cycloalkenyl" is meant a non-aromatic, optionally substituted 3– to 10–membered monocyclic or bicyclic hydrocarbon ring system having at least one carbon-carbon double bound. For example, a cycloalkenyl may have 1 or 2 carbon-carbon double bonds. Cycloalkenyls may be unsubstituted or substituted. A substituted cycloalkenyl can have, for example, 1, 2, 3, 4, 5, or 6 substituents. Exemplary cycloalkenyls include, but are not limited to,

cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, and the like.

By "effective amount" or "therapeutically effective amount" of an agent, as used herein, is that amount sufficient to effect beneficial or desired results, such as clinical results, and, as such, an effective amount depends upon the context in which it is being applied. For example, in the context of administering an agent that is an inhibitor of necroptosis, an effective amount of an agent is, for example, an amount sufficient to achieve a reduction in necroptosis as compared to the response obtained without administration of the agent.

By "ester" is meant a group having a structure selected from -OCOR', where R' is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. When R' is not H, R may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "halogen" or "halo" is meant fluorine (-F), chlorine (-Cl), bromine (-Br), or iodine (-I).

By "heteroaryl" is mean an aryl group that contains 1, 2, or 3 heteroatoms in the cyclic framework. Exemplary heteroaryls include, but are not limited to, furan, thiophene, pyrrole, thiadiazole (e.g., 1,2,3-thiadiazole or 1,2,4-thiadiazole), oxadiazole (e.g., 1,2,3-oxadiazole or 1,2,5-oxadiazole), oxazole, benzoxazole, isoxazole, isothiazole, pyrazole, thiazole, benzthiazole, triazole (e.g., 1,2,4-triazole or 1,2,3-triazole), benzotriazole, pyridines, pyrimidines, pyrazines, quinoline, isoquinoline, purine, pyrazine, pteridine, triazine (e.g, 1,2,3-triazine, 1,2,4-triazine, or 1,3,5-triazine)indoles, 1,2,4,5-tetrazine, benzo[*b*]thiophene, benzo[*c*]thiophene, benzofuran, isobenzofuran, and benzimidazole. Heteroaryls may be unsubstituted or substituted. Subsituted heteroaryls can have, for example, 1, 2, 3, 4, 5, or 6 subsitutents.

By "heterocyclic" or "heterocyclyl" is meant an optionally substituted non–aromatic, partially unsaturated or fully saturated, 3– to 10–membered ring system, which includes single rings of 3 to 8 atoms in size, and polycyclic ring

systems (e.g., bi– and tri–cyclic ring systems) which may include an aryl (e.g., phenyl or naphthyl) or heteroaryl group that is fused to a non–aromatic ring (e.g., cycloalkyl, cycloalkenyl, or heterocyclyl), where the ring system contains at least one heterotom. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized or substituted. In certain embodiments, the term heterocylic refers to a non–aromatic 5–, 6–, or 7–membered monocyclic ring wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms. Where a heterocycle is polycyclic, the constituent rings may be fused together, form a spirocyclic structure, or the polycyclic heterocycle may be a bridged heterocycle (e.g., quinuclidyl or . Exemplary heterocyclics include, but are not limited to, aziridinyl, azetindinyl, 1,3–diazatidinyl, pyrrolidinyl, piperidinyl, piperazinyl, thiranyl, thietanyl, tetrahydrothiophenyl, dithiolanyl, tetrahydrothiopyranyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyranonyl, 3,4-dihydro-2H-pyranyl, chromenyl, 2H-chromen-2-onyl, chromanyl, dioxanyl (e.g., 1,3-dioxanyl or 1,4-dioxanyl), 1,4-benzodioxanyl, oxazinyl, oxathiolanyl, morpholinyl, thiomorpholinyl, thioxanyl, quinuclidinyl, and also derivatives of said exemplary heterocyclics where the heterocyclic is fused to an aryl (e.g., a benzene ring) or a heteroaryl (e.g., a pyridine or pyrimidine) group. Any of the heterocyclic groups described herein may be unsubstituted or substituted. A substituted heterocycle may have, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "ketone" or "acyl" is meant a group having the structure -COR', where R' is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. When R' is not H, R may be unsubstituted or substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

By "nitro" is meant a group having the structure $-NO_2$.

A "pharmaceutically acceptable excipient" as used herein refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The term "pharmaceutically acceptable salt," as used herein, represents those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66:1-19. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting the free base group with a suitable organic acid. Representative acid addition salts include acetate,

adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like.

The term "pharmaceutically acceptable solvates," as used herein, refers to compounds that retain non-covalent associations to residual solvent molecules in the solid state. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Solvates include, but are not limited to, compounds that include solvent molecules in the crystal lattice following recrystallization. The molecular stoichiometry of solvation can vary from, for example, 1:1 solvent:compound to 10:1 solvent:compound. These ratios can include a mixture of associated solvent molecules. Exemplary, non-limiting examples of solvents that can form solvates with the compounds of the invention include water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, or any combination thereof.

By "pharmaceutical composition" is meant a composition containing a compound of the invention, formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Excipients consisting of DMSO are specifically excluded. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or any other formulation described herein.

By "stereoisomer" is meant a diastereomer, enantiomer, or epimer of a compound. A chiral center in a compound may have the *S*-configuration or the *R*-configuration. Enantiomers may also be described by the direction in which they rotate polarized light (i.e., (+) or (-)). Diastereomers of a compound include stereoisomers in which some, but not all, of the chiral centers have the opposite configuration as well as those compounds in which substituents are differently oriented in space (for example, *trans* versus *cis*).

Where a group is substituted, the group may be substituted with 1, 2, 3, 4, 5, or 6 substituents. Optional substituents include, but are not limited to: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, halogen; azido($-N_3$), nitro ($-NO_2$), cyano (-CN), acyloxy(-OC(=O)R'), acyl (-C(=O)R'), alkoxy (-OR'), amido (-NR'C(=O)R" or –C(=O)NRR'), amino (-NRR'), carboxylic acid ($-CO_2H$), carboxylic ester ($-CO_2R'$), carbamoyl (-OC(=O)NR'R" or -NRC(=O)OR'), hydroxy (-OH), isocyano (-NC), sulfonate ($-S(=O)_2OR$), sulfonamide ($-S(=O)_2NRR'$ or –NRS(=O)$_2$R'), or sulfonyl ($-S(=O)_2R$), where each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl. A substituted group may have, for example, 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents. In some embodiments, each hydrogen in a group may be replaced by a substituent group (e.g., perhaloalkyl groups such as

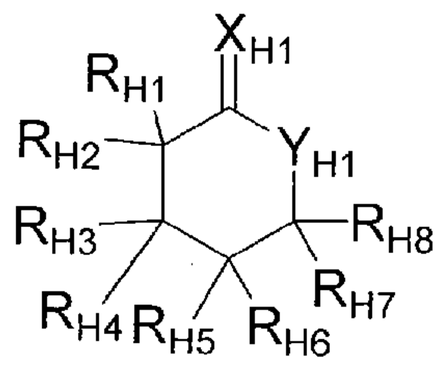
-CF_3 or -CF_2CF_3 or perhaloaryls such as -C_6F_5). In other embodiments, a substitutent group may itself be further substituted by replacing a hydrogen of said substituent group with another substituent group such as those described herein. Substituents may be further substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents as defined herein. For example, a lower C_{1-6} alkyl or an aryl substituent group (e.g., heteroaryl, phenyl, or naphthyl) may be further substituted with 1, 2, 3, 4, 5, or 6 substituents as described herein.

Detailed Description of the Invention

We have discovered a series of heterocyclic derivatives that inhibit tumor necrosis factor alpha (TNF-α)-induced necroptosis. The heterocyclic compounds of the invention include, for example, compounds of Formulas (I)-(VIII), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, and are shown to inhibit TNF-α induced necroptosis in FADD-deficient variant of human Jurkat T cells. Still other useful necrostatins include Compounds (1)-(45). Compounds of the invention can be synthesized according to methods known in the art or by the methods provided in the examples below. Pharmaceutical compositions including the compounds of the invention are also described. The invention also features kits and methods of treatment featuring the compounds and compositions of the invention.

Compounds of Formula (I)

Certain compounds of the invention can be described by Formula (I):



(I), where

each X_{H1} and X_{H2} is selected, independently, from O, S, or NR_{H9};

Y_{H1} is selected, independently, from O, S, or NR_{H10};

each R_{H1}, R_{H2}, R_{H3}, R_{H4}, R_{H5}, R_{H6}, R_{H7}, and R_{H8}, is selected, independently from H, halogen, cyano, nitro, azido, optionally substituted C_{1-6}

alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(=O)R_{H12}$, $-C(=O)OR_{H12}$, $-C(=O)NR_{H12}R_{H13}$, $-C(=S)R_{H12}$, $-C(=S)NR_{H12}R_{H13}$, $-C(=NR_{H14})R_{H12}$, $-C(=NR_{H14})NR_{H12}R_{H13}$, or $-[Z_{H1}-(CR_{H15}R_{H16})_n-\{C(=X_{H2})\}_o-Z_{H2}-R_{H17}]$, or R_{H1} and R_{H3}, or R_{H5} and R_{H7} combine to form a carbon-carbon double bond;

each Z_{H1} and Z_{H2} is selected, independently, from a single bond, O, S, or NR_{H11};

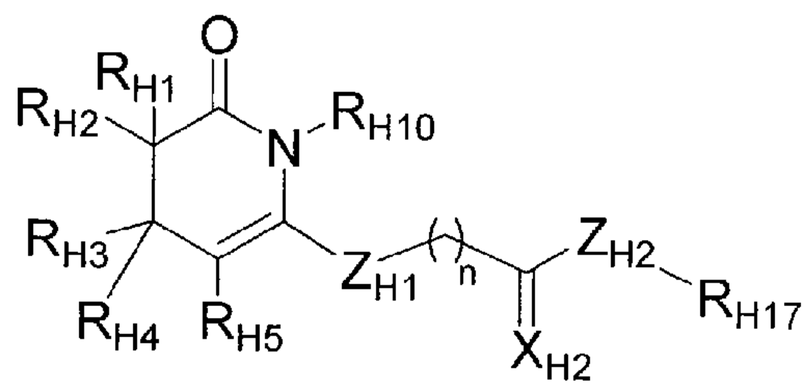
each R_{H9}, R_{H10}, R_{H11}, R_{H12}, R_{H13}, R_{H14}, R_{H15}, R_{H16}, and R_{H17}, is selected, independently from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

n is an integer between 0-6; and

o is 0 or 1;

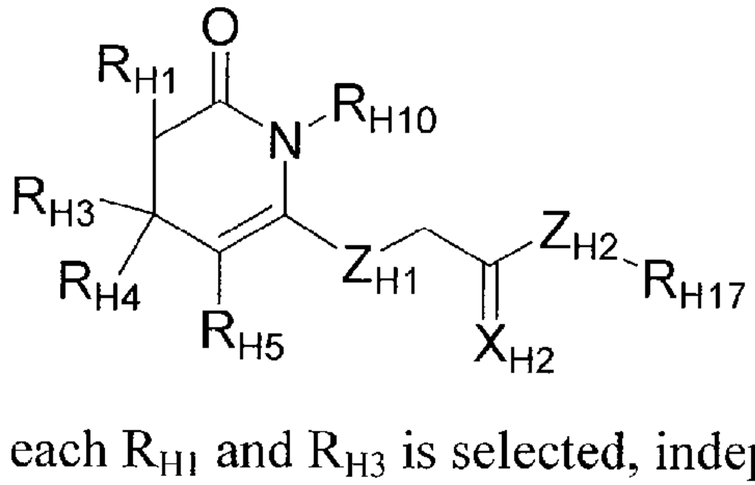
or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Certain compounds of the invention can be described by Formula (I-A):



(I-A), where each R_{H1}, R_{H2}, R_{H3}, R_{H4}, R_{H5}, R_{H10}, R_{H17}, X_{H2}, Z_{H1}, Z_{H2}, and n is as defined for Formula (I),

or by Formula (I-B)



(I-B), where

each R_{H1} and R_{H3} is selected, independently, from H, halogen, cyano, nitro, azido, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10}

cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(=O)R_{H12}$, $-C(=O)OR_{H12}$, or $-C(=O)NR_{H12}R_{H13}$, or R_{H1} and R_{H3} combine to form a carbon-carbon double bond;

each R_{H4} and R_{H17} is selected, independently, from optionally substituted aryl or optionally substituted heteroaryl;

R_{H5} is selected from H, CN, $-C(=O)OR_{H12}$, or $-C(=O)NR_{H12}R_{H13}$;

each R_{H10}, R_{H11}, R_{H12}, and R_{H13} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

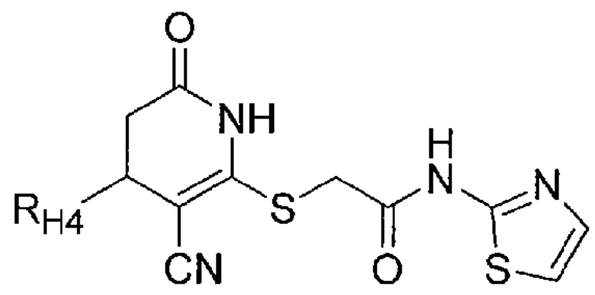
Z_{H1} is selected from a single bond or S;

Z_{H2} is selected from a single bond or NR_{H11}; and

X_{H2} is O or S;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (I), the compound has a structure according to the following formula:



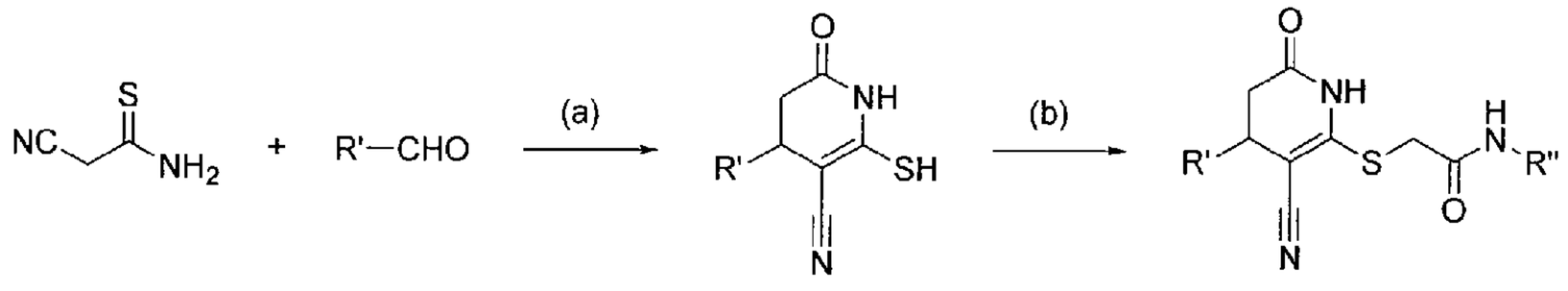
(I-C), where R_{H4} is as according to Formula (I-A) or (I-B).

In some embodiments of Formula (I), when R_{H1} is H, R_{H2} is H or CO_2Me, R_{H3} is H, R_{H4} is unsubstituted phenyl or phenyl substituted with 1, 2, or 3 substituents selected from methoxy, ethoxy, methyl, isopropyl, chloro, or fluoro, R_{H5} is CN, R_{H6} and R_{H8} is H, R_{H10} is H, X_{H1} is O, Y_{H1} is NH, and R_{H7} is $-[S-(CH_2)-\{C(=O)\}_o-Z_{H2}-R_{17}]$, Z_{H2}-R_{H17} is not OCH_3 or NH-R_{H17}, where R_{H17} is H, unsubstituted 2-thiazolyl, unsubstituted phenyl, 4-methoxyphenyl, 4-fluorophenyl, or 2,4,6-trimethylphenyl.

Compounds of Formulas (I), (I-A), (I-B), and (I-C) can be prepared according to methods known in the art. An exemplary method of synthesis that

can be used is shown in **Scheme 1** and is based on protocols disclosed in *Russian Chemical Bulletin*, 48(12): 2308-2311 (1999) and in *Chemistry of Heterocyclic Compounds*, 38(10): 1269-1275 (2002). In Scheme 1, R' and R" can be, for example, an optionally substituted aryl or an optionally substituted heteroaryl group. Still other substituent patterns can be obtained by variation of the thioamide starting material that is condensed with the aldehyde.

Scheme 1



a) Meldrum's acid, N-Methylmorpholine, EtOH, rt, 12h; b) 2-Chloro-N-R"-acetamide, EtOH, H_2O, reflux, 2min.

Compounds of Formula (I) (e.g., (I-A), (I-B), or (I-C)) or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits). Exemplary compounds useful in the methods, compositions, and kits of the invention, include but are not limited to those shown in **Table 1**. Other compounds of Formula 1 are shown in **Table 2**. In some embodiments, Formulas (I), (I-A), (I-B), or (I-C) do not include any of Compounds **(1)-(12)**.

Table 1

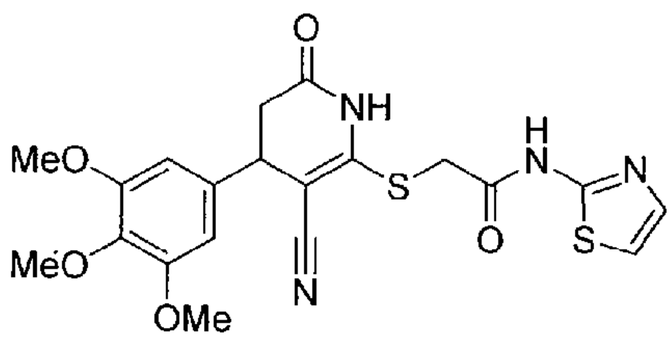
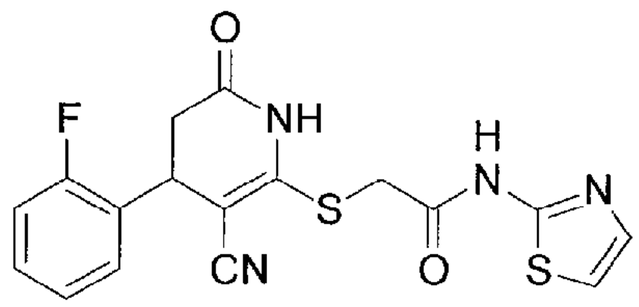
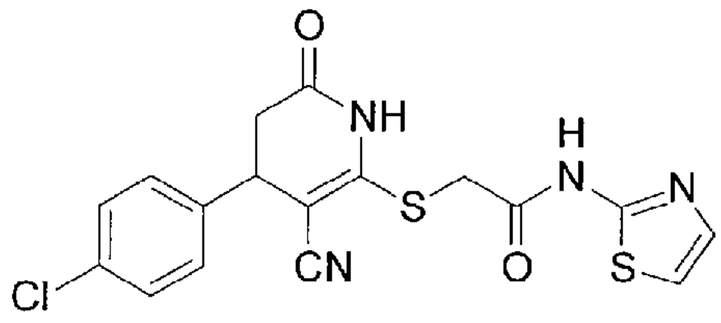
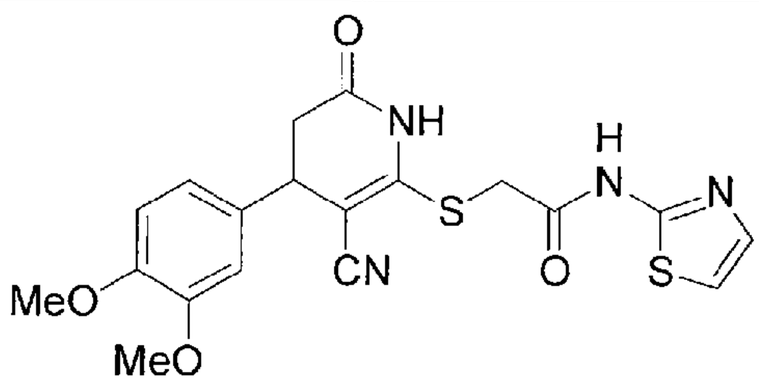
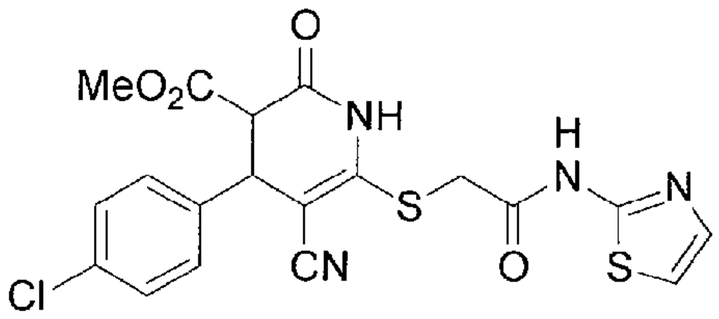
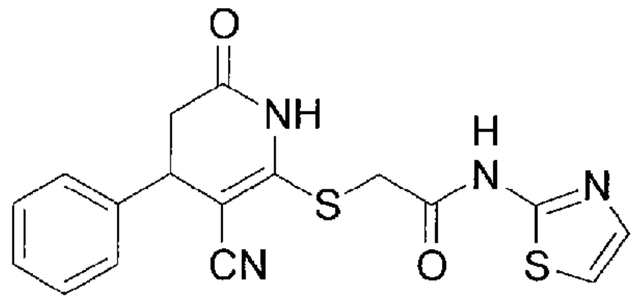
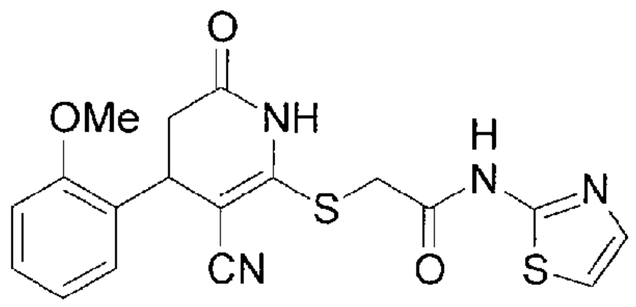
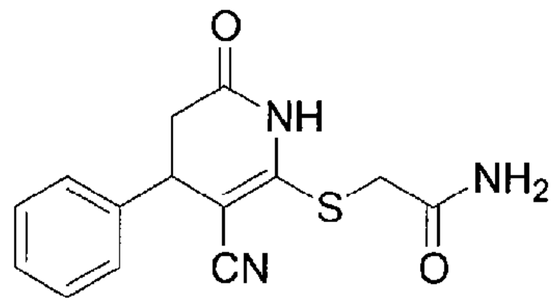
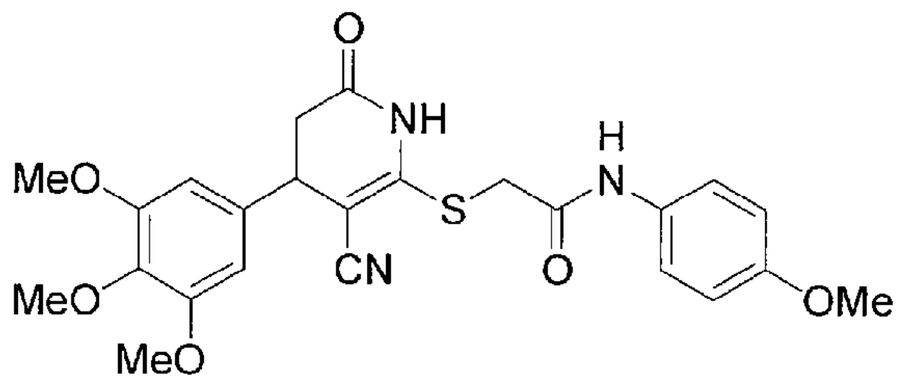
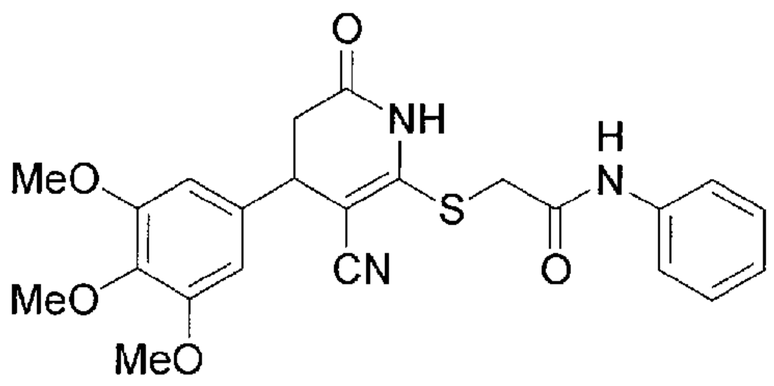
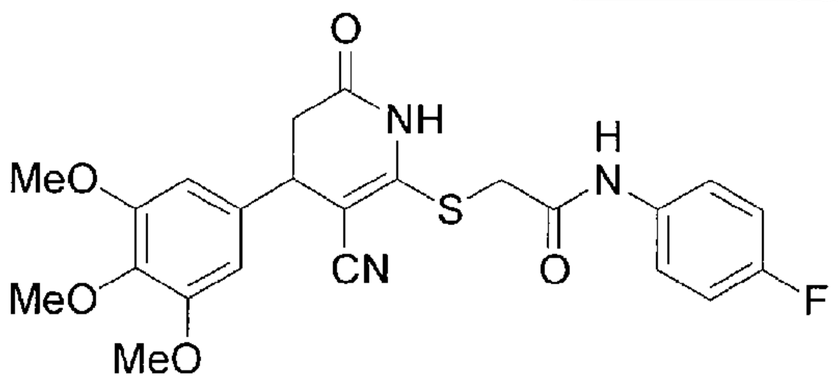
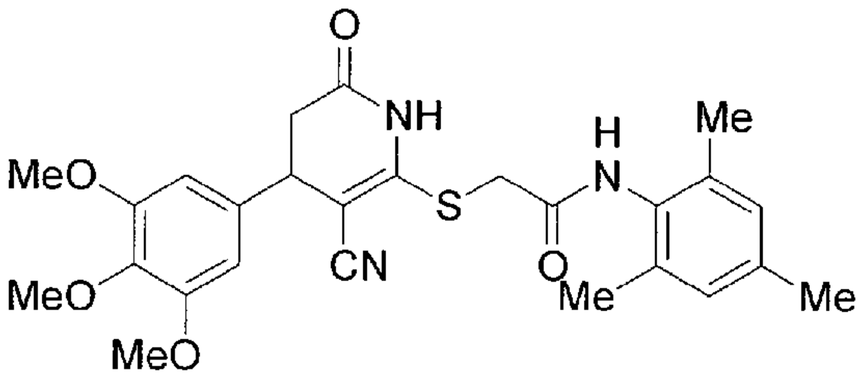
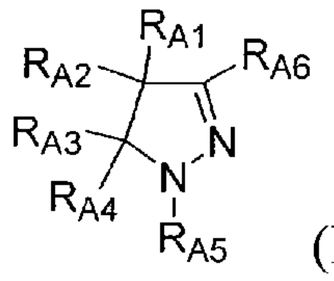
Compound	Structure
(1)	
(2)	
(3)	
(4)	
(5)	
(6)	
(7)	

Table 2

(8)	
(9)	
(10)	
(11)	
(12)	

Compounds of Formula (II)

Select compounds of the invention can be described by Formula (II)



(II), where

each R_{A1}, R_{A2}, R_{A3}, R_{A4}, R_{A5}, and R_{A6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl,

optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a group having the structure $-X_{A1}-G_{A1}-X_{A2}-C(=Y_{A1})-G_{A2}-X_{A3}-R_{A7}$, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

each X_{A1}, X_{A2}, and X_{A3} is, independently, absent or selected from –O-, -S-, or $-NR_{A8}-$;

G_{A1} is absent or $-(CR_{A9}R_{A10})_m-$;

G_{A2} is absent or $-(CR_{A11}R_{A12})_n-$;

Y_{A1} is O, S, or NR_{A13};

each R_{A8} and R_{A13} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-COR_{A14}$, $-CO_2R_{A14}$, or $-CONR_{A14}R_{A15}$;

each R_{A9}, R_{A10}, R_{A11}, and R_{A12} is selected, independently, from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{A7}, R_{A14} and R_{A15} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl; and

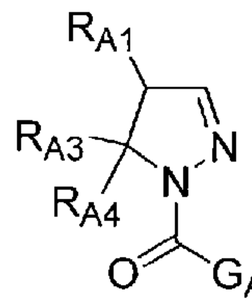
each m and n is, independently, 1, 2, or 3;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (II), when R_{A1} and R_{A4} combine to form a carbon-carbon double bond, R_{A2} is H, R_{A3} is CH_3, and R_{A6} is CO_2H, R_{A5} is not CH_2(2-chlorophenyl).

In some embodiments of Formula (II), when R_{A1} and R_{A4} combine to form a carbon-carbon double bond, R_{A2} is H, R_{A6} is CH_3 or ^tBu, and R_{A3} is $NHC(=O)NHR_{A7}$, R_{A7} is not chlorophenyl or dichlorophenyl.

Certain compounds of Formula (II) may be described further according to Formula (II-A)



(II-A), where

each R_{A1}, R_{A3}, R_{A4}, and R_{A7} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

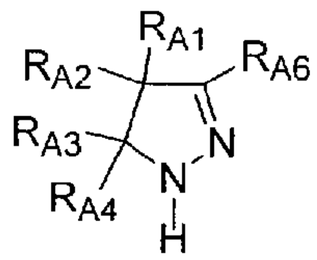
G_{A2} is absent or is $-(CR_{A11}R_{A12})_n-$;

X_{A3} is absent or is O, S, or NR_{A8};

each R_{A11}, R_{A12}, and R_{A8} is selected, independently, from H or optionally substituted C_{1-6} alkyl; and

n is 1 or 2;

or according to Formula (II-B)



(II-B), where

R_{A5} is H;

each R_{A1}, R_{A2}, R_{A3}, R_{A4}, and R_{A6} is selected, independently, from H, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)-X_{A3}-R_{A7}$, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

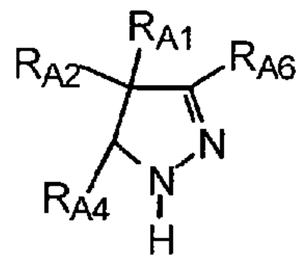
each R_{A7} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each X_{A3} is, independently, absent, -O-, or $-NR_{A8}-$,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (II) (e.g., (II-A) and (II-B)), when one of R_{A1} and R_{A4} is H and the other is selected from H or CO_2Et, and R_{A3} is unsubstituted phenyl, G_{A2}-X_{A3}-R_{A7} is not NHC_6H_5, NH(p-C_6H_4F), NH(p-C_6H_4OH), NH(p-C_6H_4OMe), NH(3-OH-4-Cl-C_6H_4), -CH_2(O-*p*-C_6H_4Me), -CH_2(4-ethylpiperazinyl), -CH_2S(2-phenyltetrazolyl), -CH_2S(4-chlorophenyl), -CH_2S(2-benzothiazolyl), -CH_2S(2-(N-methylimidazolyl)), -CH_2S(4,6-dimethylquinazolinyl), adamantyl, or optionally substituted oxiranyl.

Other compounds of Formula (II) include compounds of Formula (II-C):



(II-C), where

each R_{A1}, R_{A2}, R_{A4}, and R_{A6} is selected, independently, from H, -C(=O)-X_{A3}-R_{A7}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

each X_{A3} is, independently, absent, -O-, or -NR_{A8}-,

each R_{A8} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -COR_{A14}, -CO_2R_{A14}, or -$CONR_{A14}R_{A15}$; and

each R_{A7}, R_{A14} and R_{A15} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl.

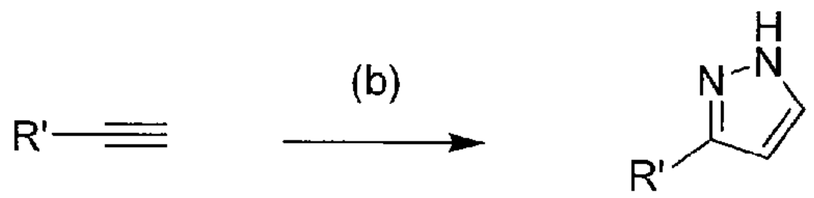
In some embodiments of Formula (II-C), wherein when R_{A1} and R_{A4} combine to form a carbon-carbon double bond and R_{A2} is H, R_{A6} is not 4-chlorophenyl, 4-methoxyphenyl, or 4-(NH$CO_2{}^t$Bu)phenyl. In other embodiments, when R_{A1} is H, R_{A4} is H or CO_2Et, R_{A2} is unsubstituted phenyl,

R_{A6} is not –C(=O)-(unsubstituted phenyl) or –C(=O)-(4-methylphenyl). In still other embodiments, when R_{A1} is H, R_{A4} is –C(=O)-(unsubstituted phenyl), R_{A2} is 4-chlorophenyl, R_{A6} is not CO_2Et.

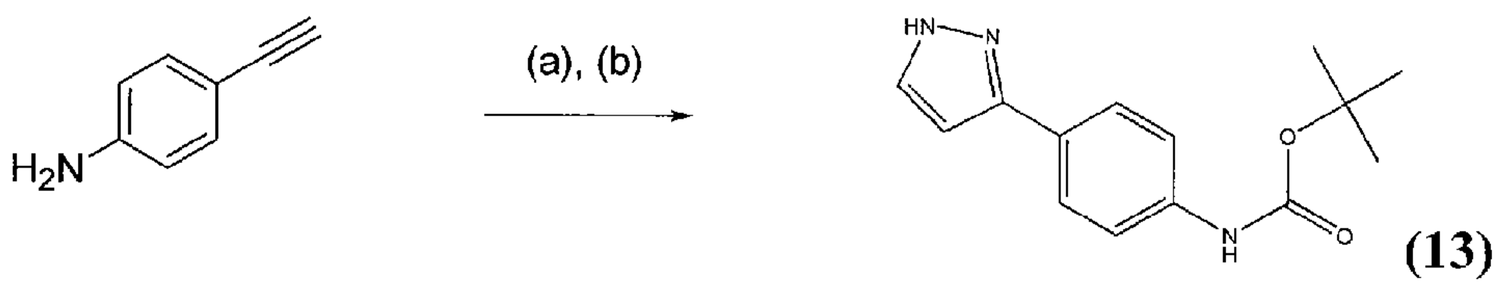
Compounds of Formula (II) (e.g., (II-A)-(II-C)) can be prepared according to methods known in the art. Exemplary methods of synthesis are shown in **Schemes 2-5**.

Scheme 2

(2A)



(2B)

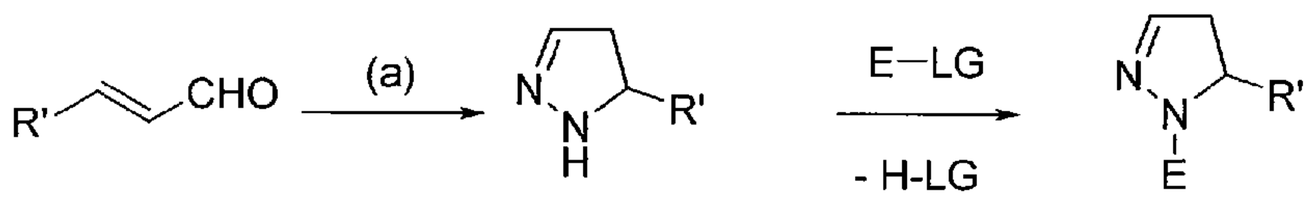


(13)

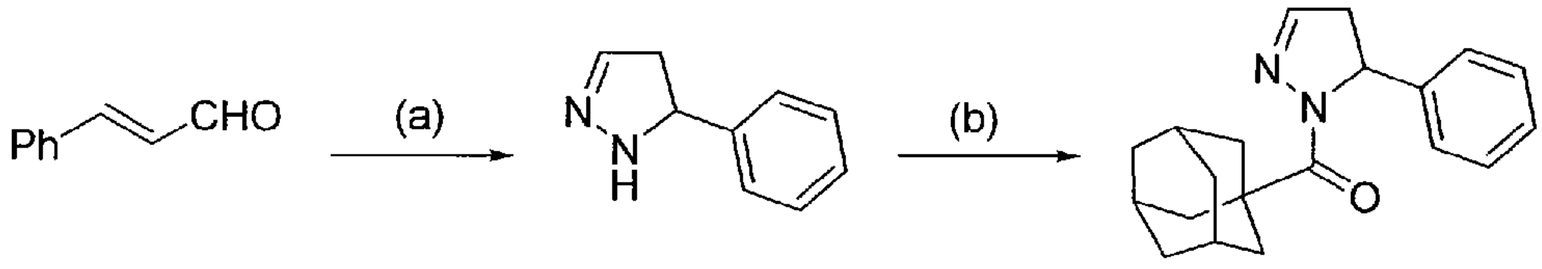
a) Boc_2O, THF, 3h, reflux; b) trimethylsilyl diazomethane, DMF, 100°C, 60h.

Scheme 2A shows a method that can be used to prepare pyrazole compounds of Formula (II). Terminal alkynes can be reacted with trimethylsilyldiazomethane (TMS-diazomethane) to afford compounds of Formula (II) where R_{A1} and R_{A4} combine to form a carbon-carbon double bond and R' can be, for example, optionally substituted aryl or optionally substituted heteroaryl. **Scheme 2B** shows the preparation of Compound **(13)** using the method in Scheme 2A in which the aniline $–NH_2$ group is protected prior to the reaction with TMS-diazomethane.

Scheme 3



(3A)



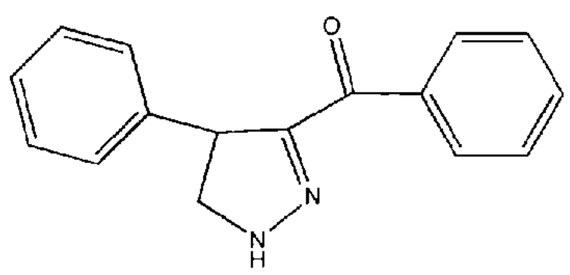
(3B)

(14)

a) N_2H_4, EtOH; b) 1-Adamantane carbonyl chloride, heat, 5min.

Scheme 3A depicts another method that can be used to synthesize pyrazoline compounds of Formula (II) according to methods described in *J. Chem. Soc.* 4686-90 (1952) and *J. Med. Chem.* 2127-2137 (2006). For example, substituted acroleins (e.g., R' can be optionally substituted aryl or optionally substituted heteroaryl) can be treated with ethanolic hydrazine (**Step (a)**) to afford a pyrazoline intermediate. The pyrazoline can then be treated with an electrophilic compound having a suitable leaving group (e.g., alkyl halides, acid cholorides. or acid anhydrides) and an optional chemical promotoer to afford *N*-substituted pyrazolines. **Scheme 3B** shows a method that can be used to prepare **Compound (14)** where an acid chloride can be used in Step (b) as shown.

Scheme 4



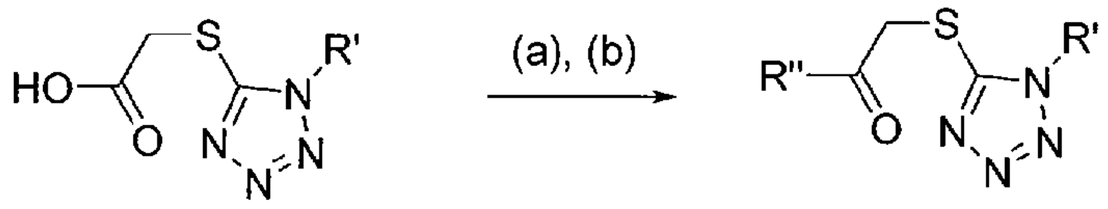
(15)

Scheme 4 shows Compound **(15)** which can be prepared according to the procedure described in *J. Am. Chem. Soc.*, page 165 (1943). This method can also be used to prepare other pyrazoline compounds of Formula (II), where

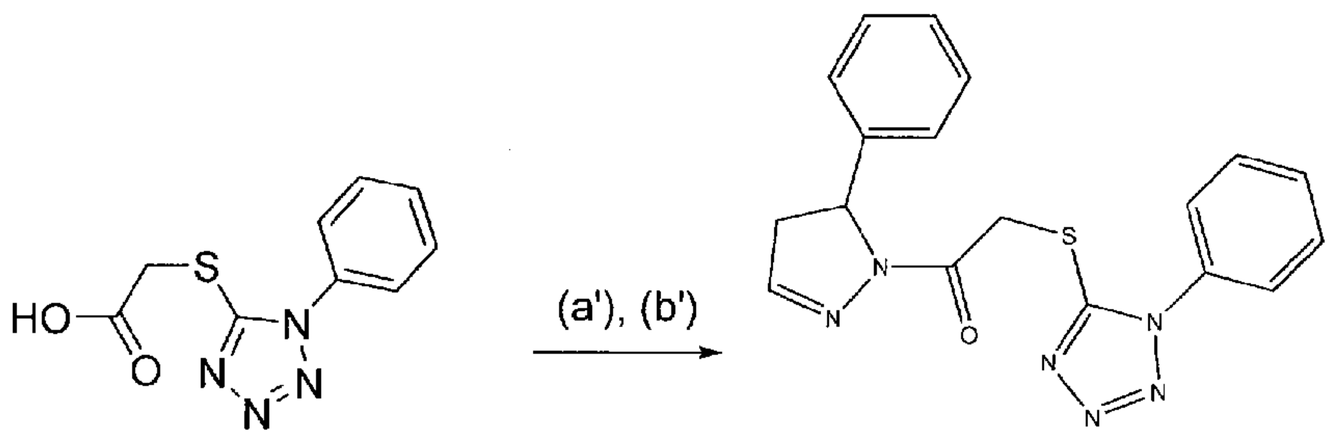
R_{A6} is -C(=O)-R_{A7} and R_{A2} and R_{A7} are, independently, optionally substituted aryl or optionally substituted heteroaryl.

Scheme 5

(5A)



(5B)



(16)

a) PCl_5, $CHCl_3$, Toluene, 3.5h; b) R", 70°C.

Scheme 5A depicts a method by which tetrazole compounds of Formula (II) can be prepared using methods described in WO2005115147 and in *J. Med. Chem.*, 4686-90 (1952). For example, a tetrazole compound that includes a carboxylic acid group can be activated (e.g., treatment with PCl_5 as in Step (a)) and subsequently treated with a nucleophile R" as in Step (b). **Scheme 5B** shows that 5-Phenyl-4,5-dihydro-1H-pyrazole can be used as the nucleophile in step (b') to afford Compound **(16)**.

Compounds of Formula (II) (e.g., (II-A) and (II-B) and compounds **(13)**-(16)), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits). Additional exemplary compounds useful in, for example, the methods, compositions, and kits of the invention, include but are not limited to those shown in **Table 3**. Other compounds of Formula (II) are shown in **Table 4**. In some embodiments, Formula (II), (II-A), and (II-B) do not include any of compounds **(13)-(26)**.

Table 3

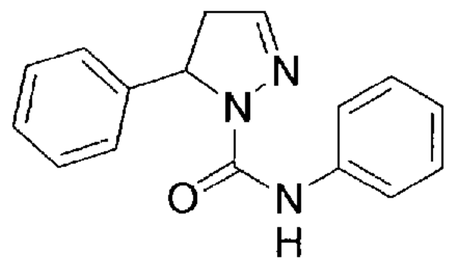
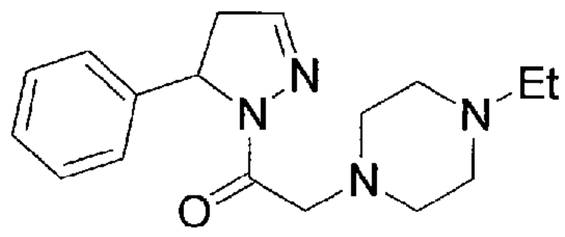
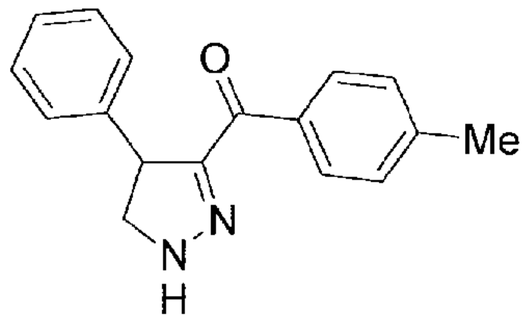
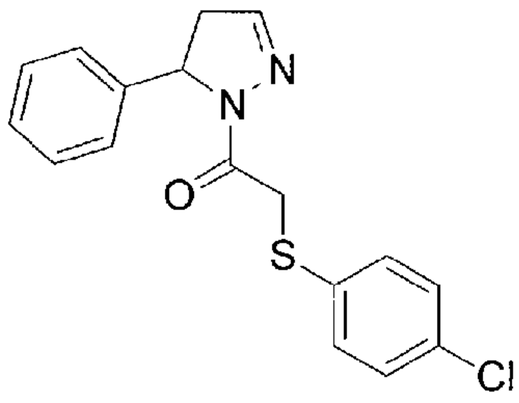
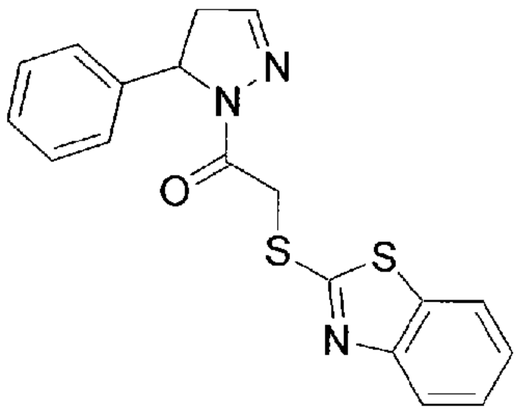
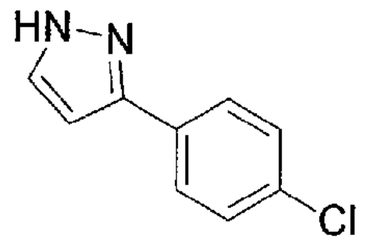
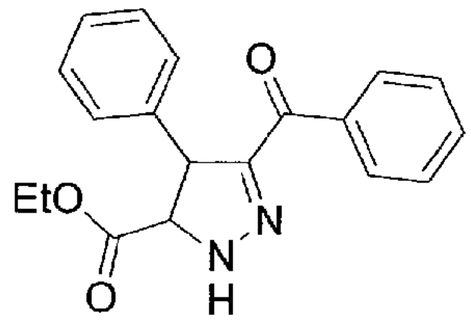
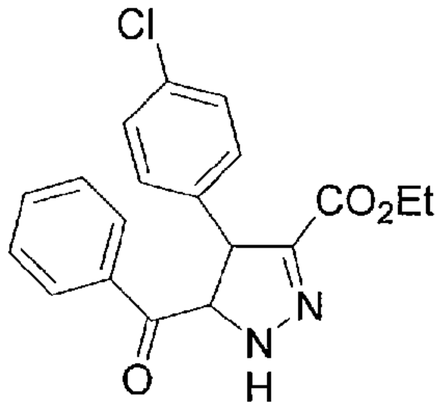
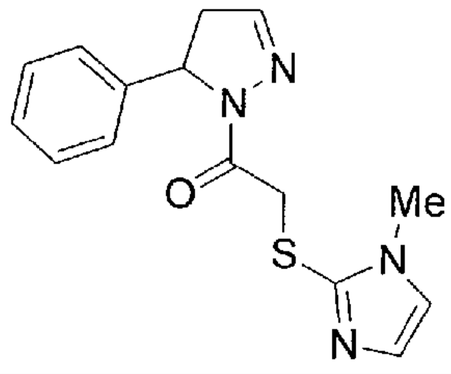
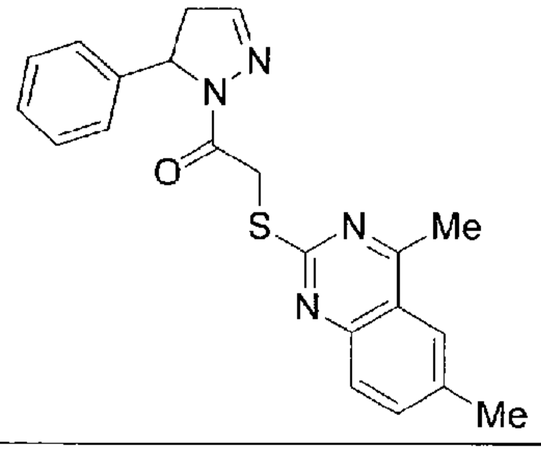
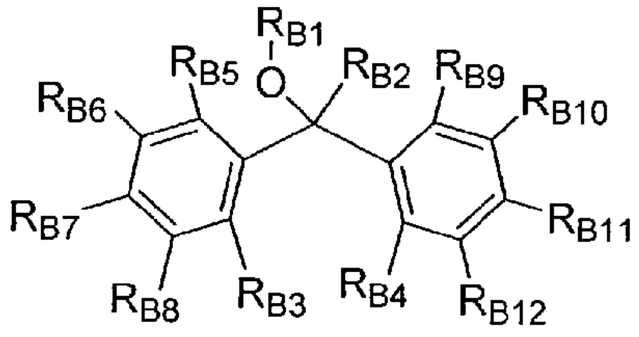
Compound	Structure
(17)	
(18)	
(19)	
(20)	
(21)	

Table 4

Compound	Structure
(22)	
(23)	
(24)	
(25)	
(26)	

Compounds of Formula (III)

Select compounds of the invention can be described by Formula (III)



(III), where

R_{B1} is selected from H, optionally substituted C_{1-6} alkyl, $-C(=O)R_{B18}$, $-C(=O)OR_{B18}$, or $-C(=O)NR_{B18}R_{B19}$;

R_{B2} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R_{B3} and R_{B4} is selected, independently from H, optionally substituted C_{1-6} alkyl, or R_{B3} and R_{B4} combine to form a bridging group having the structure $-(CH_2)_n-(CR_{B13}=CR_{B14})_o-(CH_2)_p-$;

each n, o, and p is, independently, 0 or 1;

each R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H, halogen, –CN, $-NO_2$, $-N_3$, $-R_{B13}$, $-OR_{B13}$, $-SR_{B13}$, $-NR_{B13}R_{B14}$, $-C(=O)R_{B15}$, $-C(=O)OR_{B15}$, $-C(=O)NR_{B15}R_{B16}$, $-OC(=O)R_{B15}$, $-OC(=O)OR_{B15}$, $-OC(=O)NR_{B15}R_{B16}$, $-NR_{B15}C(=O)R_{B15}$, $-NR_{B15}C(=O)OR_{B16}$, $-NR_{B15}C(=O)NR_{B16}R_{B17}$, $-C(=S)R_{B15}$, $-C(=S)NR_{B15}R_{B16}$, $-NR_{B15}C(=S)R_{B16}$, $-NR_{B15}C(=S)NR_{B16}R_{B17}$, $-C(=NR_{B13})NR_{B15}R_{B16}$, $-NR_{B15}C(=NR_{B13})R_{B16}$, $-NR_{B15}C(=NR_{B13})NR_{B16}R_{B17}$;

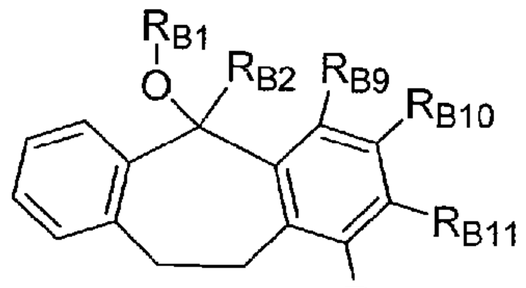
each R_{B13} and R_{B14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R_{B18}$, $-C(=O)OR_{B18}$, or $-C(=O)NR_{B18}R_{B19}$;

each R_{B15}, R_{B16}, R_{B17}, R_{B18}, and R_{B19} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

where when each n, o, and p is 0, R_{B3} and R_{B4} combine to form a single bond,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Select compounds of Formula (III) can also be described by Formula (III-A)

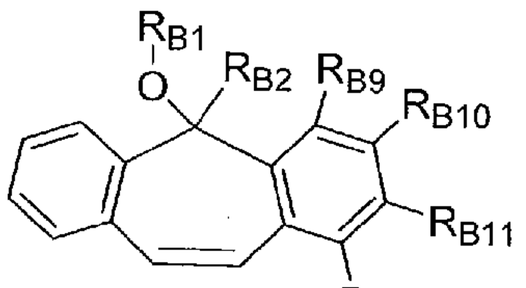


(III-A), where R_{B1} is as described in Formula (III), R_{B2} is ethyl, ethenyl, or ethynyl and each R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H and halogen,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{B1} is H.

Still other compounds of Formula (III) are described by Formula (III-B)



(III-B), where R_{B1} is as described in Formula (III), R_{B2} is ethyl, ethenyl, or ethynyl and each R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H and halogen,

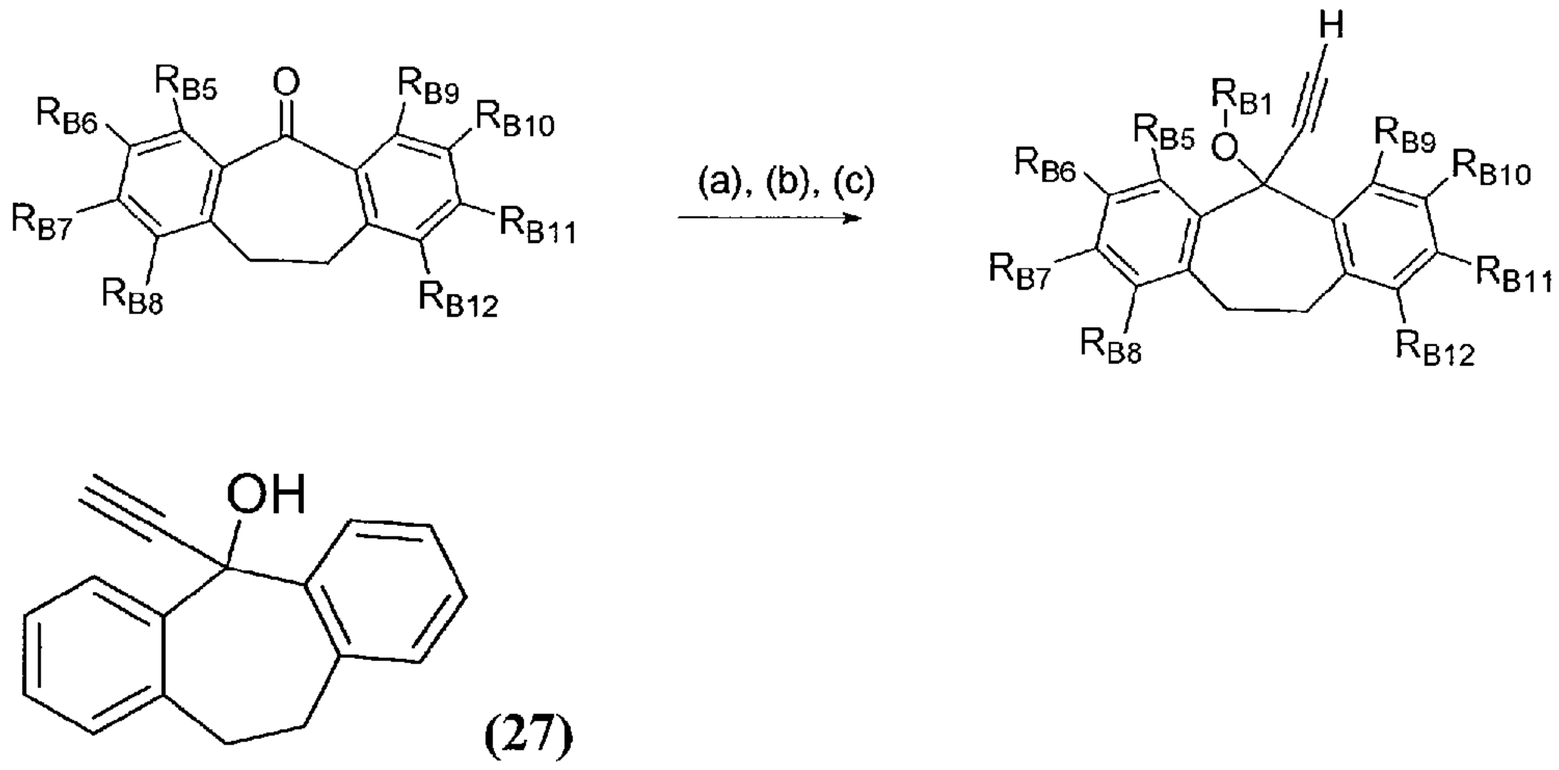
or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, R_{B1} is H.

In some embodiments of Formula (III), R_{B1} is not H or CH_3 when R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B9}, R_{B10}, R_{B11}, and R_{B12} are each H, R_{B2} is ethyl, ethenyl, ethynyl, propynyl, 2-haloethynyl, -(C≡CC(-OH)(CH_3)$_2$), and when R_{B3} and R_{B4} are each H or combine to form a bond, –CH_2CH_2- or –CH=CH-. In other embodiments of Formula (III), R_{B1} is not H when R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B10}, and R_{B11} are each H, at least one of R_{B9} or R_{B12} is fluoro, R_{B2} is ethynyl, and when R_{B3} and R_{B4} combine to form –CH_2CH_2-. In still other embodiments of

Formula (III), R_{B1} is not H when R_{B6}, R_{B7}, R_{B8}, R_{B10}, and R_{B11} are H and one or two of R_{B6}, R_{B8}, R_{B10}, and R_{B12} is halogen, nitro, or methyl.

Scheme 6



(6A) **(6B)** **(27)**

(a) *n*-BuLi/Trimethylsilylacetylene, THF, 0°C; THF, rt then reflux; (b) quench with H^+ or electrophile R_{B1}-X; (c) 0.1M NaOH, MeOH, rt, 6h.

Scheme 6A depicts a method by which compounds of Formula (III) can be prepared. A ketone derivative can be treated with an anionic carbon nucleophile (e.g., lithium trimethylsilylacetylide formed in step (a)). The resulting alkoxide can be trapped using a protic quench or by the addition of an electrophilic reagent. Finally, the trimethylsilyl group can be deprotected using basic conditions. If desired, the alkyne group can be further manipulated (e.g., subjectcd to hydrogenation conditions to afford the corresponding alkene or alkyl group or treated with a metal catalyst/and organic electrophile in cross-coupling reactions). **Scheme 6B** shows **Compound (27)**, which can be prepared using these conditions.

Compounds of Formula (III) (c.g., (III-A) and (III-B) and compound (**27**)), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits). Additional exemplary compounds useful in, for example, the methods, compositions, and kits of the invention, include but are not limited to those shown in **Table 5**. Other compounds of Formula (III)

include Compounds **(35)-(36)**, **(39)-(40)**, and **(42)-(47)** shown in **Table 6**. In some embodiments, Formula (III) does not include any of Compounds **(27)-(33)**, **(35)-(36)**, **(39)-(40)**, or **(42)-(47)**.

Table 5

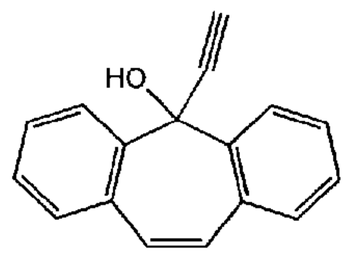
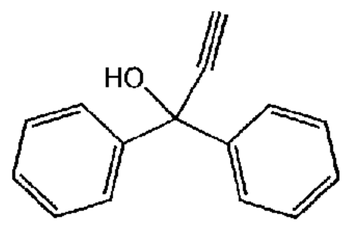
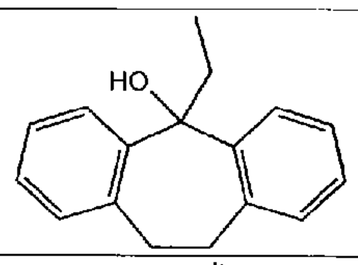
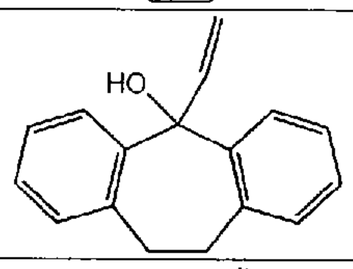
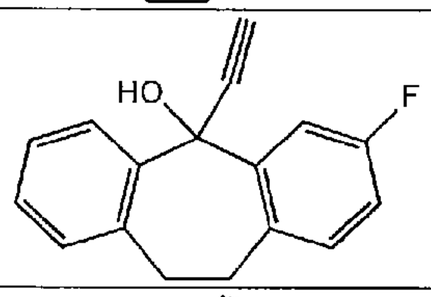
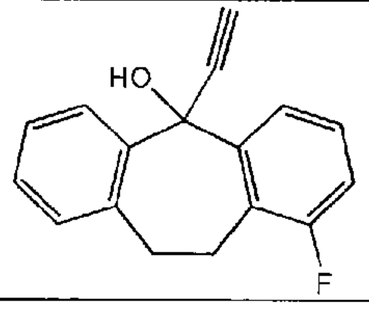
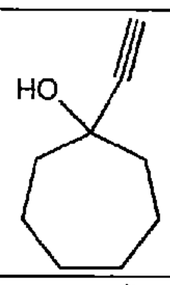
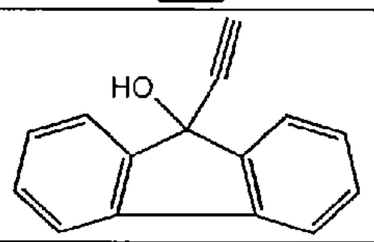
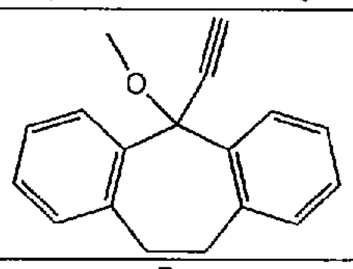
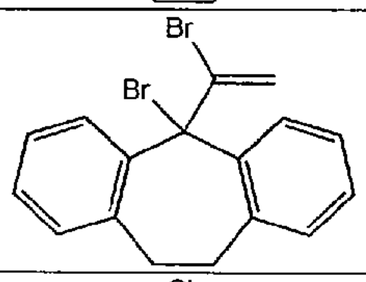
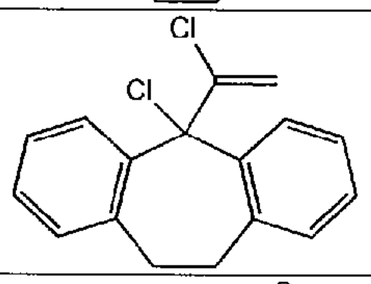
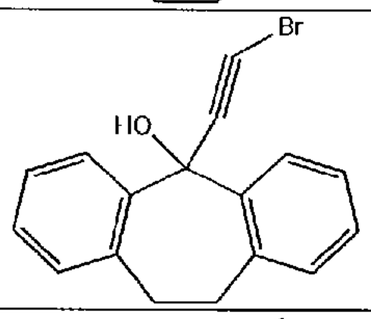
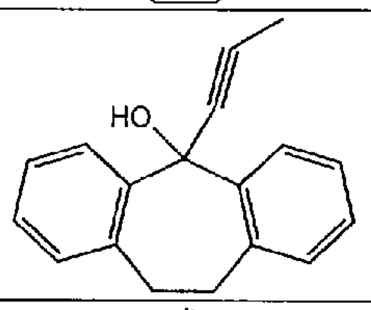
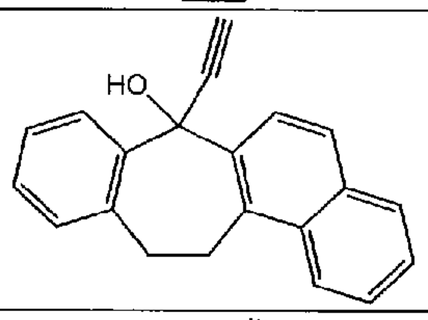
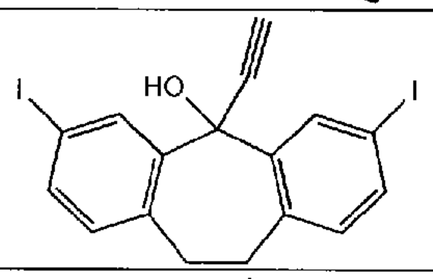
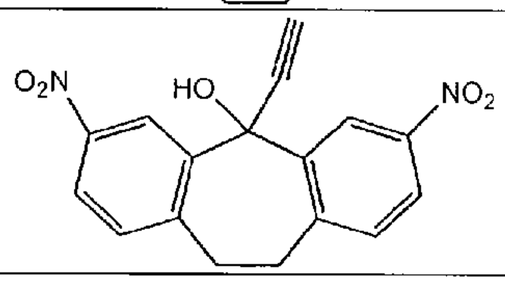
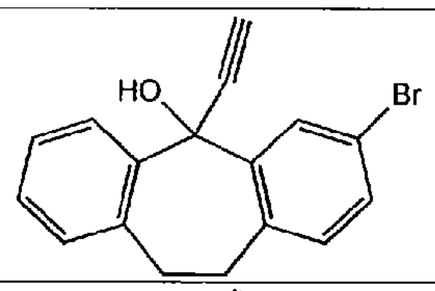
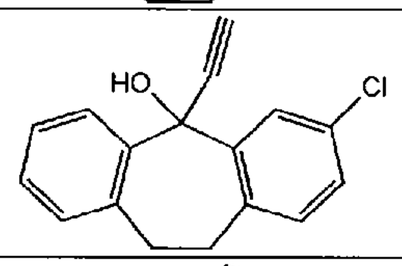
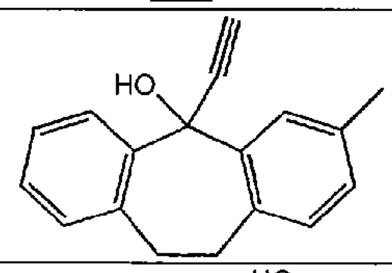
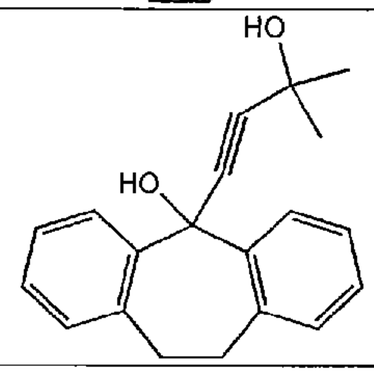
Compound	Structure
(28)	
(29)	
(30)	
(31)	
(32)	
(33)	

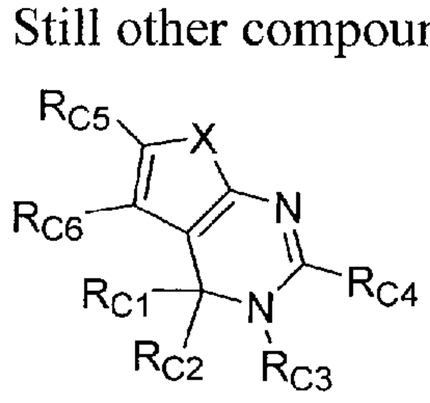
Table 6

Compound	Structure
(34)	
(35)	
(36)	
(37)	
(38)	
(39)	
(40)	
(41)	
(42)	
(43)	

Compound	Structure
(44)	
(45)	
(46)	
(47)	

Compounds of Formula (IV)

Still other compounds can be described according to Formula (IV)

 (IV), where

each R_{C1}, R_{C2}, and R_{C3} is selected, independently, from H, optionally substituted C_{1-6} alkyl, -Y-R_{C7}, or R_{C1} and R_{C2} combine to form a (=O) or a (=S) group, or R_{C1} and R_{C3} combine to form a carbon-nitrogen double bond;

R_{C4} is selected from H, halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or -C(=O)ZR_{C8},

each R_{C5} and R_{C6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, or R_{C1} and R_{C2} combine to form an optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{C7}, R_{C8}, R_{C9}, R_{C10}, R_{C11}, and R_{C12} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

X is $-CR_{C11}=CR_{C12}-$, O, S, or NR_{C9};

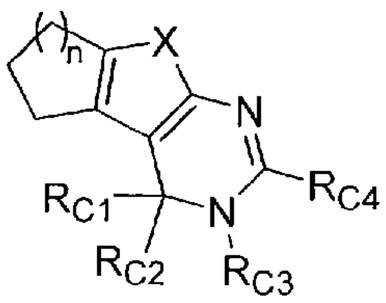
Y is, independently, a single bond, $(CR_{C8}R_{C9})_n$, O, S, or NR_{C10};

Z is a single bond, O, S, or NR_{C10};

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (IV), when X is S, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} combine to form unsubstituted cyclopentyl, R_{C3} is not $-CH_2-R_{C7}$, where R_{C7} is unsubstituted phenyl, unsubstituted naphthyl, unsubstituted 8-quinolyl, unsubstituted 2-oxoquinolyl, or phenyl having 1 or 2 substituents selected from F, OMe, Me, CN, or Cl. In other embodiments of Formula (IV), when X is S, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} are each Me, R_{C3} is not $-CH_2-R_{C7}$, where R_{C7} is unsubstituted phenyl. In other embodiments of Formula (IV), when X is CH=CH, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4}, R_{C5} and R_{C6} are H, R_{C3} is not $-CH_2$(4-halophenyl).

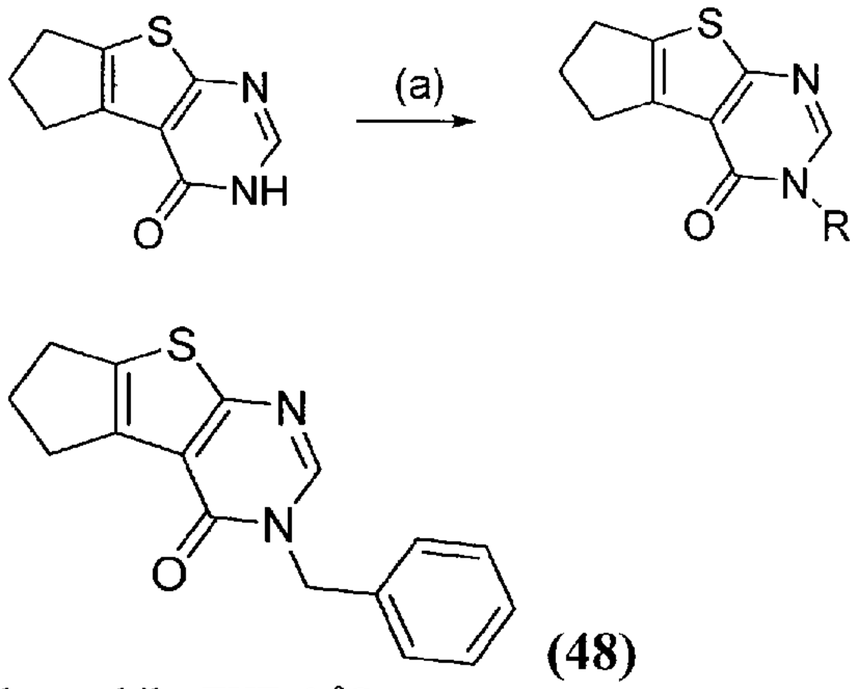
Select compounds of Formula (IV) can also be described by Formula (IV-A)



(IV-A), where X, R_{C1}, R_{C2}, R_{C3}, and R_{C4} are as defined for Formula (IV) and n is an integer between 0-3,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Scheme 7

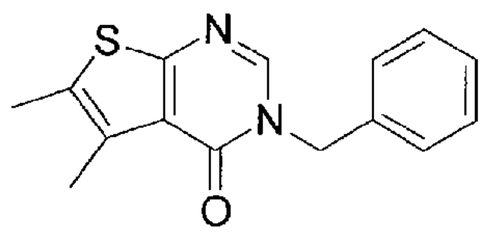
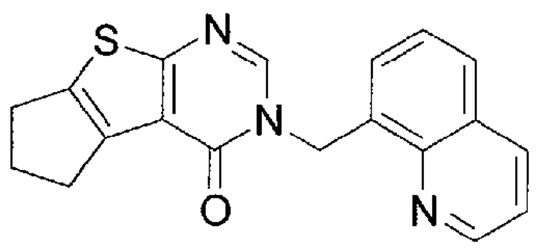
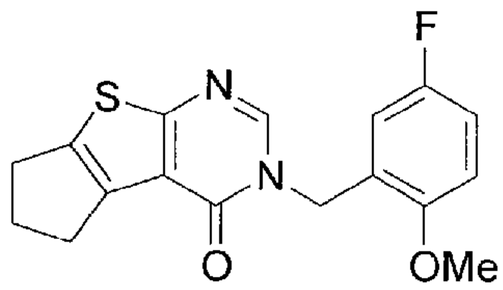
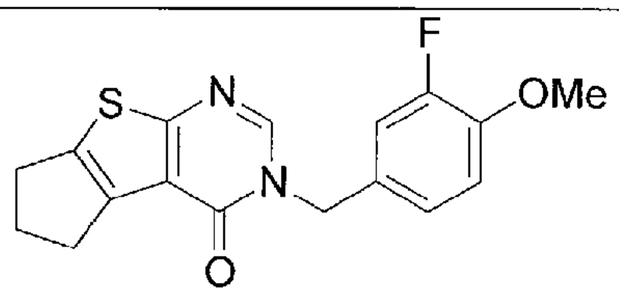
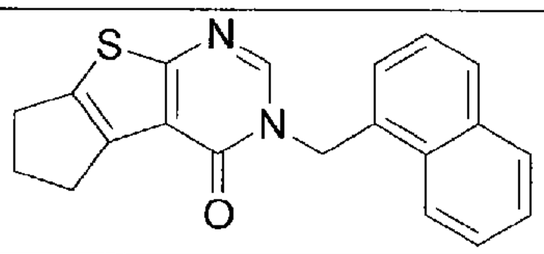
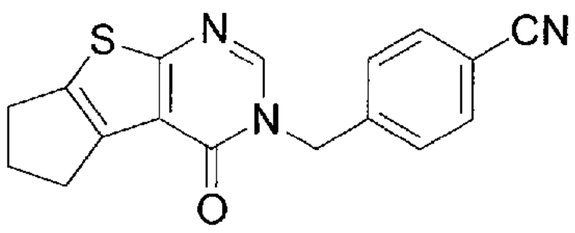
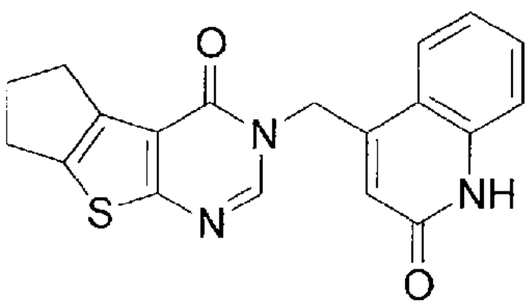


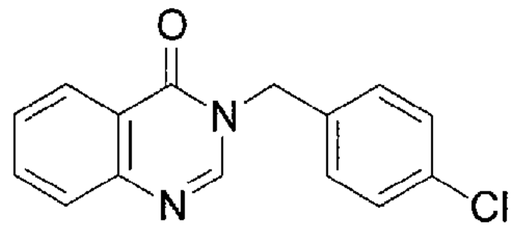
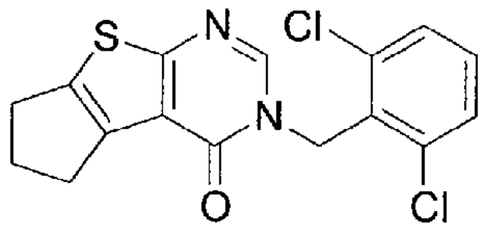
a) NaH, electrophile, THF, 0 °C

Scheme 7A depicts a method by which compounds of Formula (IV) (e.g., compounds of Formula (IV-A)) can be prepared. A heterocyclic derivative can be deprotonated using a base such as NaH and subsequently treated with an electrophile (e.g., an alkyl halide such as benzyl bromide, an acid chloride, or an acid anhydride) to afford a compound of Formula (IV) such as Compound **(48)** shown in **Scheme 7B**.

Compounds of Formula (IV) (e.g., (IV-A) and Compound (**48**)), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits). Additional exemplary compounds useful in, for example, the methods, compositions, and kits of the invention, include but are not limited to those shown in **Table 7**. In some embodiments, Formula (IV) does not include any of Compounds **(48)**-**(57)**.

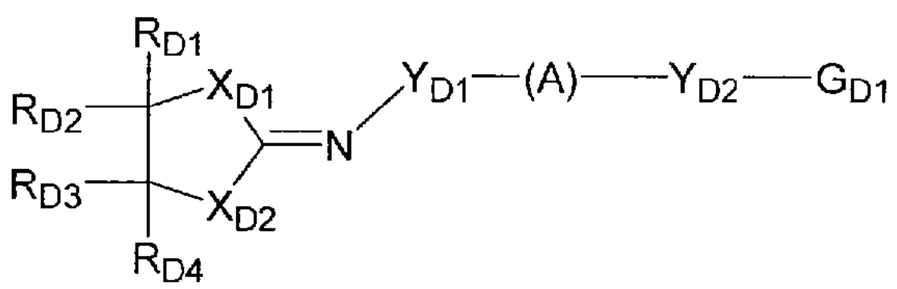
Table 7

Compound	Structure
(49)	
(50)	
(51)	
(52)	
(53)	
(54)	
(55)	

Compound	Structure
(56)	
(57)	

Compounds of Formula (V)

Other compounds of the invention can be described by Formula (V)



(V), where

each X_{D1} and X_{D2} is selected, independently, from O, S, NR_{D5}, or $CR_{D6}R_{D7}$;

Y_{D1} is selected from a covalent bond, -C(=O)-, -S(=O)-, or -$S(=O)_2$-;

Y_{D2} is selected from a covalent bond, -C(=O)-, -OC(=O)-, -NR_{D8}C(=O)-, -S(=O)-, -$S(=O)_2$-, -OS(=O)-, -$OS(=O)_2$-, -NR_{D8}S(=O)-, - $NR_{D8}S(=O)_2$-, or -C(=S)-;

A is selected from optionally substituted aryl or optionally substituted heteroaryl;

G_{D1} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, OR_{D9}, or $NR_{D9}R_{D10}$;

each R_{D1}, R_{D2}, R_{D3}, R_{D4}, R_{D6}, R_{D7}, is selected, independently, from H, halogen, CN, NC, N_3, NO_2, OR_{D11}, SR_{D11}, $NR_{D11}R_{D12}$, -COR_{D13}, -CO_2R_{D13}, -$CONR_{D13}R_{D14}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or

optionally substituted heteroaryl, or R_{D1} and R_{D4}, or R_{D1} and R_{D5}, or R_{D1} and R_{D6}, or R_{D3} and R_{D5}, or R_{D3} and R_{D6} combine to form a double bond;

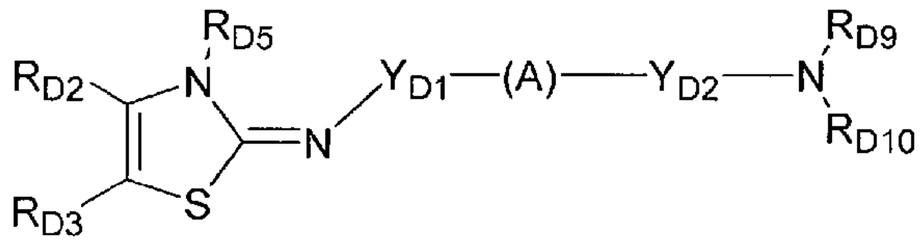
each R_{D5}, R_{D8}, R_{D9}, R_{D10}, R_{D13}, R_{D14}, R_{D15}, and R_{D16} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{D9} and R_{D10} combine to form a heterocyclyl;

each R_{D11} and R_{D12} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-COR_{D15}$, $-CO_2R_{D15}$, $-CONR_{D15}R_{D16}$, $-S(=O)R_{D15}$, $-S(=O)OR_{D15}$, $-S(=O)NR_{D15}R_{D16}$, $-S(=O)_2R_{D15}$, $-S(=O)_2OR_{D15}$, $-S(=O)_2NR_{D15}R_{D16}$;

where Y_{D1} and Y_{D2} are each covalently bound to a carbon center in A;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Still other compounds of Formula (V) can be described by Formula (V-A)



(V-A), where

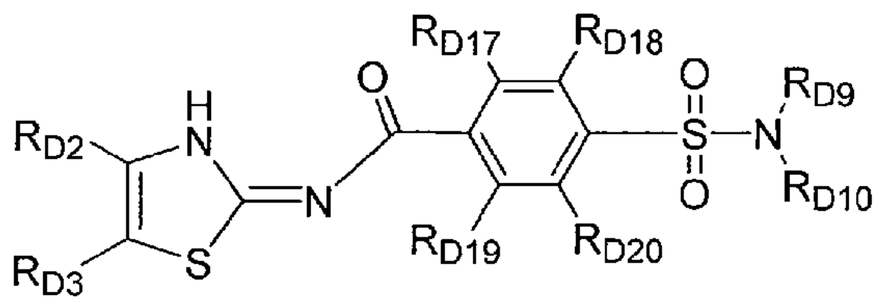
each Y_{D1} and Y_{D2} is selected, independently, from $-C(=O)-$ or $-S(=O)_2-$;

A is phenyl having 0, 1, 2, 3, or 4 additional substituents;

R_{D2} and R_{D3} are selected, independently from H, halogen, CN, NC, N_3, NO_2, $-COR_{D13}$, $-CO_2R_{D13}$, $-CONR_{D13}R_{D14}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{D5}, R_{D9}, R_{D10}, R_{D13}, and R_{D14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{D9} and R_{D10} combine to form a heterocyclyl;

or by Formula (V-B)



(V-B), where

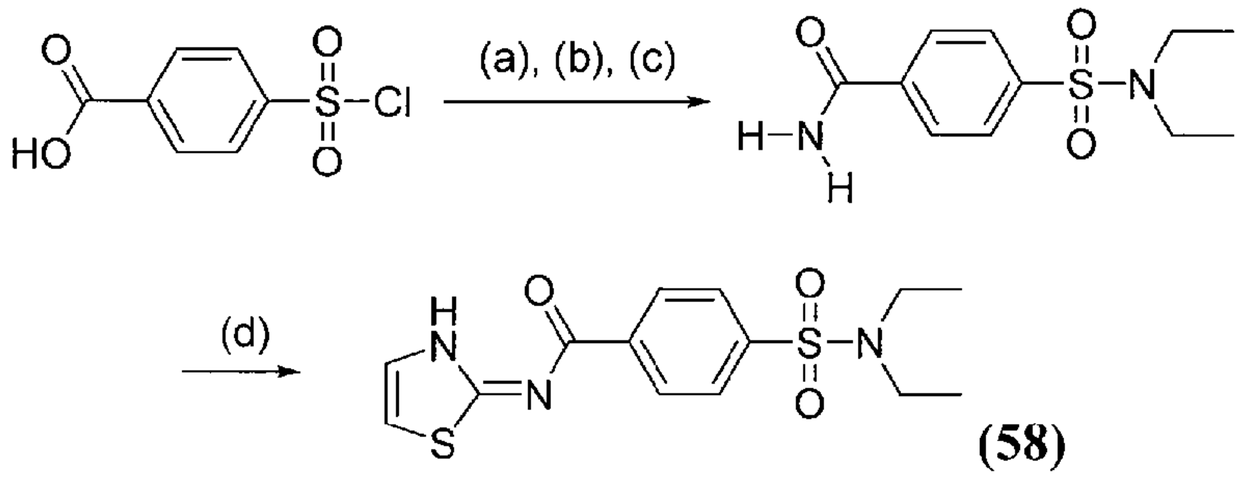
each R_{D2}, R_{D3}, R_{D17}, R_{D18}, R_{D19}, and R_{D20}, is selected, independently from H, halogen, CN, NC, N_3, NO_2, $-COR_{D13}$, $-CO_2R_{D13}$, $-CONR_{D13}R_{D14}$, optionally substituted C_{1-6} alkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R_{D9} and R_{D10} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, or optionally substituted aryl, or R_{D9} and R_{D10} combine to form a heterocyclyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (V), when R_{D1} and R_{D4} combine to form a double bond, R_{D2} and R_{D3} are H, X_{D1} is NH, X_{D2} is S, Y_{D1} is –(C=O)-, Y_{D2} is $-(SO_2)-$, G_{D1} is $-N(Et)_2$, and A is phenyl having no additional substituents, Y_{D1} and Y_{D2} are not para to each other.

Scheme 8



(58)

(a) Et_2NH, NaOH, H_2O, 3.5h then acidify; (b) H_2SO_4, MeOH, reflux; (c) NH_3 in MeOH. rt; (d) 3H-Thiazol-2-one, $TiCl_4$, Et_2O, Hexane, -30°C.

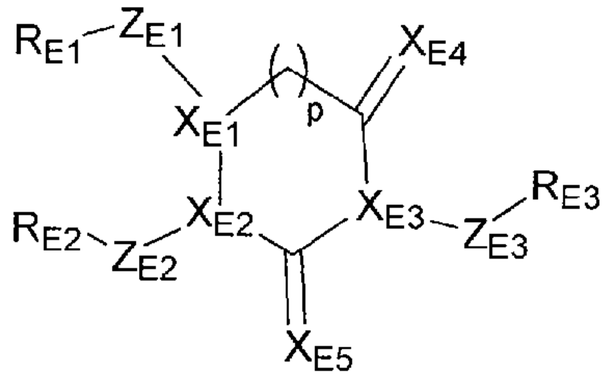
Compounds of Formula (V) (e.g., compounds of Formula (V-A) or (V-B)) can be prepared, for example, by treating an aryl or heteroaryl compound that has two electrophilic groups successively with nucleophilic reagents to afford the desired compound. For example, as shown in **Scheme 8** and using procedures adapted from *Heterocyclic Communications*, 12(6): 453-456 (2006)

and *Organic Synthesis, Collective Vol. 6*, page 818, the difunctional benzene derivative 4-CO_2Hphenylsulfonyl chloride can be treated with a nucleophile such as diethylamine to afford the corresponding sulfonamide. This compound can then be esterified prior to treatment with a second nucleophile (e.g., methanolic ammonia). Finally, the compound afforded by step (c) can then be condensed with a carbonyl-containing compound to afford compounds of Formula (V) such as **Compound (58)**.

Compounds of Formula (V) (e.g., (V-A) and (V-B) and compound (34)), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits). In some embodiments, Formulas (V), (V-A), and (V-B) do not include Compounds (**58**).

Compounds of Formula (VI)

Still other compounds of the invention can be described by Formula (VI)



(VI), where

each X_{E1} and X_{E3} is selected, independently, from N or CR_{E4};

each X_{E4} and X_{E5} is selected, independently, from O, S, or NR_{E5};

X_{E2} is selected from O, S, or N;

each Z_{E1}, Z_{E2}, and Z_{E3} is selected, independently, from a single bond, $-(CR_{E6}R_{E7})_n-$, -C(=O)-, -S(=O)-, or $-S(=O)_2-$, or Z_{E1}-R_{E1} and Z_{E2}-R_{E2} combine to form a double bond;

each R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{E5}, R_{E6}, and R_{E7} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl,

optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

p is 0 or 1; and

n is an integer between 1-6; and

where when X_{E2} is O or S, Z_{E2}-R_{E2} is not present;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, each R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{E5}, R_{E6}, and R_{E7} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl

In some embodiments, R_{E3} is selected from substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In some embodiments of Formula (VI), when p is 0, X_{E1} is CH, -Z_{E1}-R_{E1} is $-CH_2$(indol-3-yl), X_{E4} and X_{E5} are O, and X_{E2}-Z_{E2}-R_{E2} is NH, X_{E3}-Z_{E3}-R_{E3} is not -$NCH_2(p\text{-}ClC_6H_4)$ or $-NCH_2CH_2O(p\text{-}FC_6H_4)$.

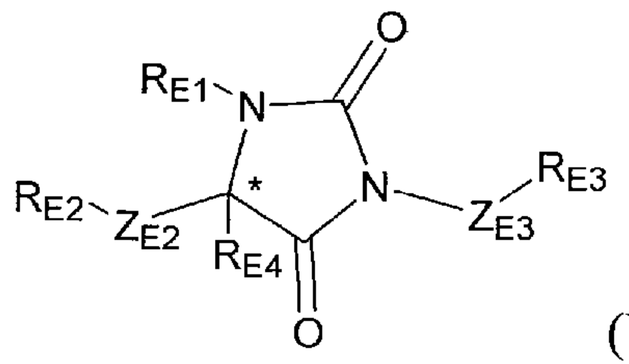
In other embodiments, when X_{E1}-Z_{E1}-R_{E1} is NH, X_{E2}-Z_{E2} is CH-CH_2, R_{E2} is unsubstituted 3-indolyl, p is 0, X_{E4} is S, X_{E5} is O, X_{E3} is N, and Z_{E3} is CH_2, R_{E3} is not -CH_2CH_2(4-morpholine).

In still other embodiments, when X_{E1}-Z_{E1}-R_{E1} is NH, X_{E2}-Z_{E2} is CH-CH_2, R_{E2} is unsubstituted or substituted 3-indolyl, p is 0 or 1, both X_{E4} and X_{E5} are O or X_{E4} is S and X_{E5} is O, X_{E3} is N, and Z_{E3} is CH_2, R_{E3} is not H, unsubstituted C_{1-6} alkyl, or -$CH_2CH{=}CH_2$.

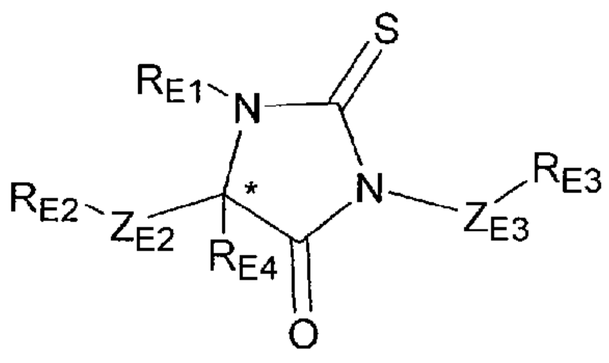
In any of the compounds of Formula (VI) described herein (e.g., any compound having a structure according to Formulas (VI), (VI-A), (VI-B), (VI-C), or (VI-D)), the R_{E3} group can be unsubstituted. In some embodiments, a substituted R_{E3} group includes 1, 2, 3, 4, or 5 substituents selected from, for example, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, azido(-N_3), alkoxy (-OR'), amido (-NR'C(=O)R"

or –C(=O)NRR'), amino (-NRR'), carbamoyl (-OC(=O)NR'R" or -NRC(=O)OR'), hydroxy (-OH), or isocyano (-NC), where each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In other embodiments, the substituted R_{E3} group includes 1, 2, 3, or 4 substituents that are electron donating groups (e.g., hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, and amino groups).

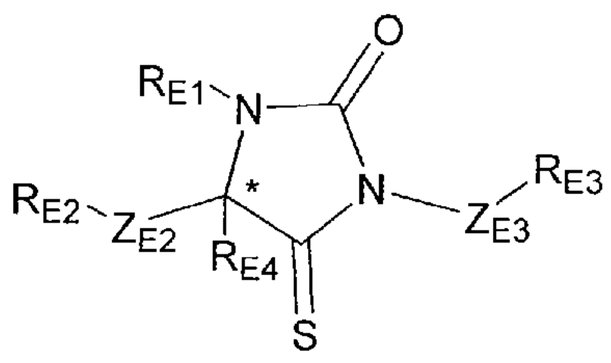
Certain compounds of Formula (VI) may be described by Formula (VI-A) or Formula (VI-B)



(VI-A),



(VI-B-1), or



(VI-B-2),wherein

each Z_{E2} and Z_{E3} is selected, independently, from a single bond, $-(CR_{E6}R_{E7})_n-$, -C(=O)-, or R_{E1} and Z_{E2}-R_{E2} combine to form a double bond;

each R_{E1}, R_{E2}, R_{E3}, and R_{E4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{E6} and R_{E7} is selected, independently, from H or optionally substituted C_{1-6} alkyl; and

n is an integer between 1-6;

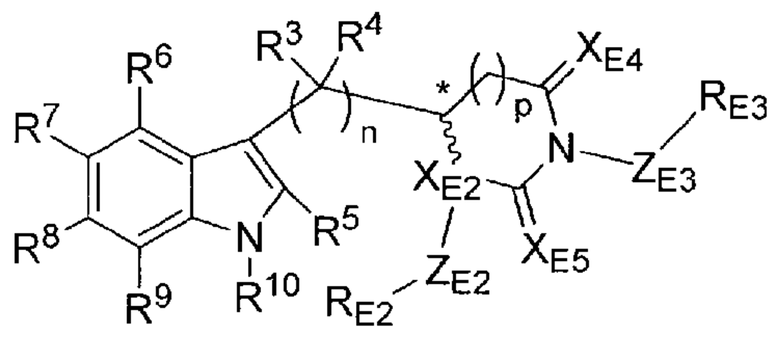
or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments, each R_{E1}, R_{E2}, R_{E3}, and R_{E4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In some embodiments, R_{E3} is selected from substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

In some embodiments of Formula (VI-A), when R_{E1} and R_{E4} are H, Z_{E2} and Z_{E3} are each CH_2, and R_{E2} is unsubstituted 3-indolyl, R_{E3} is not 4-chlorophenyl.

In certain embodiments, the compounds of Formula (VI) are described by the following formula:



(VI-C), where

each X_{E4} and X_{E5} is, independently, O or S;

X_{E2} is O or N;

each Z_{E2} and Z_{E3} is selected, independently, from a single bond or $-(CR_{E6}R_{E7})_n-$;

each R_{E2} and R_{E3} is, independently, H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each R^3 and R^4 is, independently, H, halogen, or optionally substituted C_{1-6} alkyl;

each R^5, R^6, R^7, R^8, and R^9 is selected, independently, from H, halogen, CN, NO_2, OR^{13}, $NR^{13}R^{14}$, COR^{15}, CO_2R^{15}, optionally substituted C_{1-6} alkyl, or optionally substituted aryl;

R^{10} is selected from H, halogen, CN, NO_2, OR^{13}, $NR^{13}R^{14}$, COR^{15}, CO_2R^{15}, optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted alkenyl, or optionally substituted alkynyl;

each R^{13} and R^{14} is selected, independently, from H, COR^{16}, CO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R^{11}, R^{12}, R^{15}, and R^{16} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

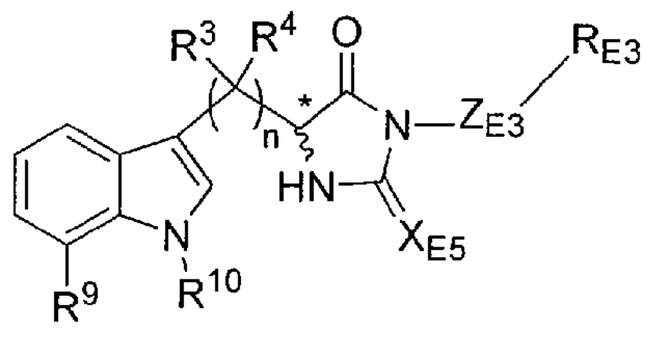
where, independently, n is 0, 1, 2, 3, 4, or 5, and p is 0 or 1;

or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

In some embodiments, p is 0.

In some embodiments, R_{E3} is selected from substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

Select compounds of Formula (VI-C) can also be described by Formula (VI-D):



(VI-D), where

X_{E5} is O or S;

$-Z_{E3}-R_{E3}$ is optionally substituted C_{1-4} alkaryl;

each R^3, R^4, and R^{10} is, independently, H or optionally substituted C_{1-6} alkyl;

R^9 is H, halogen, CN, NO_2, OR^{13}, $NR^{13}R^{14}$, COR^{15}, CO_2R^{15}, or optionally substituted C_{1-6} alkyl;

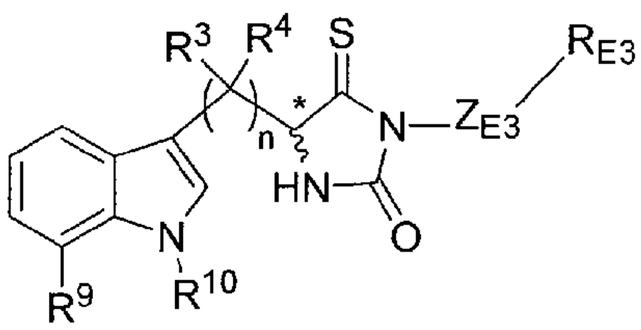
each R^{13} and R^{14} is selected, independently, from H, COR^{16}, CO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R^{11}, R^{12}, R^{15}, and R^{16} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

where n is 1 or 2;

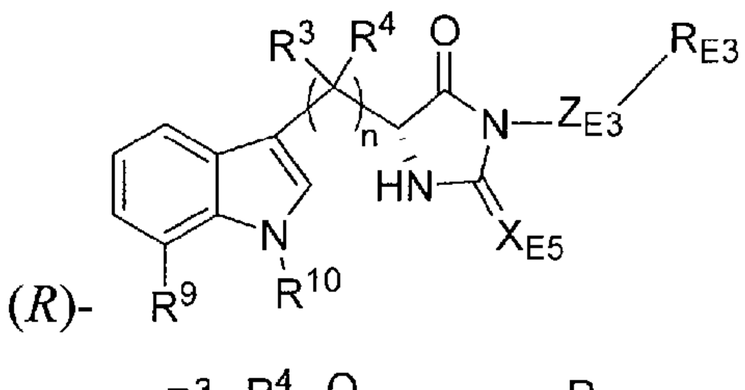
or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

In some embodiments, the compound has a structure according to the following formula:

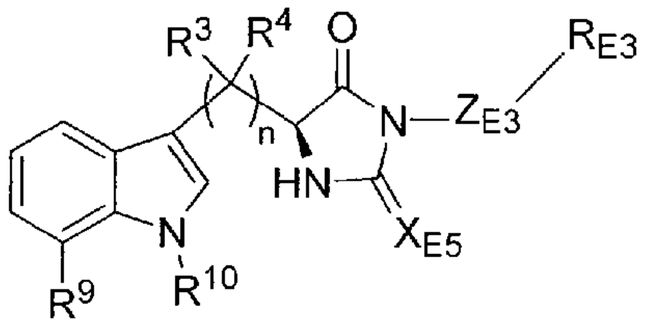


(VI-E), or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof, where n, Z_{E3}, R_{E3}, R^3, R^4, R^9, and R^{10} are as defined for Formula (IV-D).

In the compounds of the invention, the sp^3-hybridized carbon to which G is attached (e.g., the chiral center marked with an asterisk in any of Formulas (VI-A), (VI-B-1), (VI-B-2), (VI-C), (VI-D), or (VI-E)) can have the (*R*)- or the (*S*)-configuration. For example, compounds of the invention include



(*R*)- (VI-D-1) and (*S*)-



(VI-D-2),

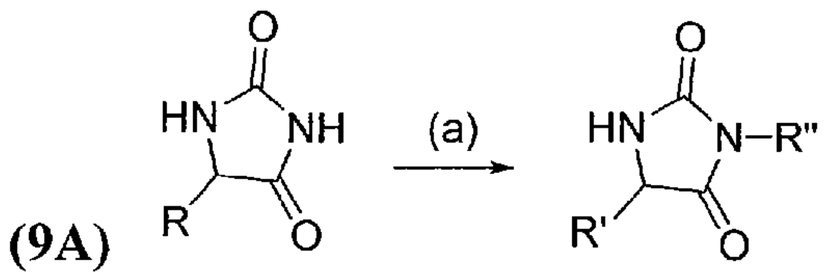
or any pharmaceutically acceptable salt or solvate thereof.

In any embodiment of Formulas (VI-C), (VI-D), or (VI-E), n = 1 and R^3 and R^4 are each H. In another embodiment, R^{10} is H or CH_3. In still other embodiments, R^9 is H, halogen, optionally substituted C_{1-6} alkyl, OH, or -O-(optionally substituted C_{1-6} alkyl).

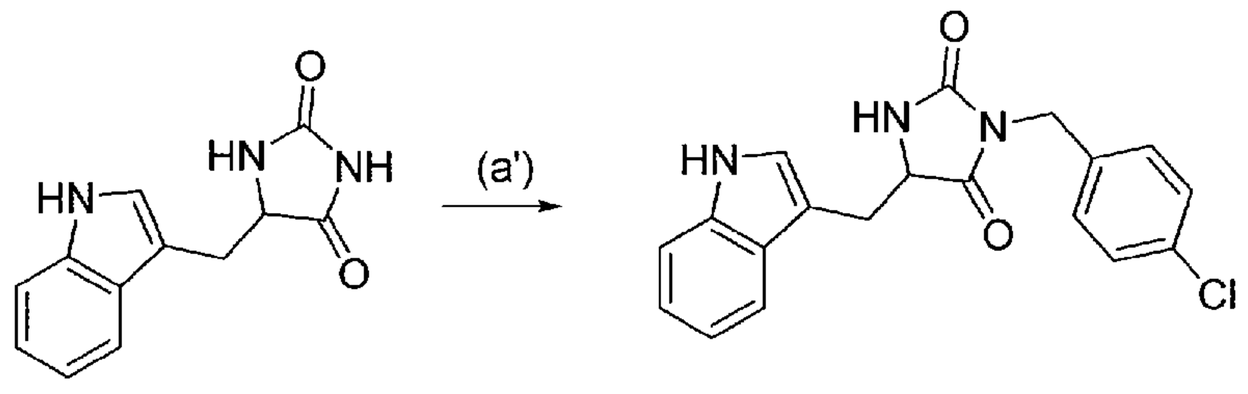
In any embodiment of Formulas (VI-C), (VI-D), or (VI-E), $-Z_{E3}-R_{E3}$ is optionally substituted benzyl. In one embodiment, $-Z_{E3}-R_{E3}$ is unsubstituted benzyl. In another embodiment, $-Z_{E3}-R_{E3}$ is benzyl having 1, 2, 3, 4, or 5 substituents. In some embodiments, the substituents are selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, azido($-N_3$), alkoxy (-OR'), amido (-NR'C(=O)R" or –C(=O)NRR'), amino (-NRR'), carbamoyl (-OC(=O)NR'R" or -NRC(=O)OR'), hydroxy (-OH), and isocyano (-NC), as described herein. In a further embodiment, $-Z_{E3}-R_{E3}$ is CH_2-(p-XC_6H_4), where X is halogen. In some embodiments, X is F or Cl.

In any of the embodiments described herein, one or both of $-Z_{E3}$ and R_{E3} do not include substituents selected from the group consisting of: halogen (e.g., F, Cl, Br, or I); nitro ($-NO_2$), cyano (-CN), acyloxy(-OC(=O)R'), acyl (-C(=O)R'), carboxylic acid ($-CO_2H$), carboxylic ester ($-CO_2R'$), sulfonate ($-S(=O)_2OR$), sulfonamide ($-S(=O)_2NRR'$ or $–NRS(=O)_2R'$), or sulfonyl ($-S(=O)_2R$), where each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, as described herein.

Scheme 9



(9A)



(9B) **(59)**

(a) electrophile R"-X, KOH, EtOH, H_2O, 100°C, 12h; (a') electrophile = 4-chlorobenzylbromide

Compounds of Formula (VI) (e.g., compounds of Formulas (VI-A), (VI-B), (VI-C), or (VI-D)) can be prepared, for example, by treating hydantoin compound that has, for example, a substituent R at the 5-position with a base followed by trapping with an electrophilic reagent (**Scheme 9A**). For example, **Scheme 9B** shows that the synthesis of **Compound (59)** can be achieved by the use of 4-chlorobenzylbromide as the electrophile.

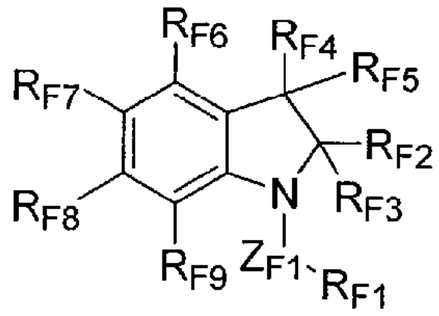
In some embodiments, Formula (VI) (e.g., compounds of Formulas (VI-A), (VI-B), (VI-C), or (VI-D)) does not include any of the compounds or formulas disclosed in U.S. Patent Nos. 6,756,394 and 7,253,201, in U.S. Patent Publication No. 20050119260, and in pending U.S. Application Nos. 12/077,320 and 12/086,792, each of which is hereby incorporated by reference.

Compounds of Formula (VI) (e.g., (VI-A)-(VI-D) and compound (59)), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits).

In some embodiments, Formula (VI) does not include compound **(59)**.

Compounds of Formula (VII)

Still other compounds can be described according to Formula (VII)



(VII), where

Z_{F1} is selected from a single bond, $-(CR_{F10}R_{F11})_n-$, -C(=O)-, -S(=O)-, or $-S(=O)_2-$;

each R_{F1}, R_{F2}, R_{F4}, R_{F10}, R_{F11}, R_{F12}, and R_{F13}, is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{F2} and R_{F4} combine to form a carbon-carbon double bond;

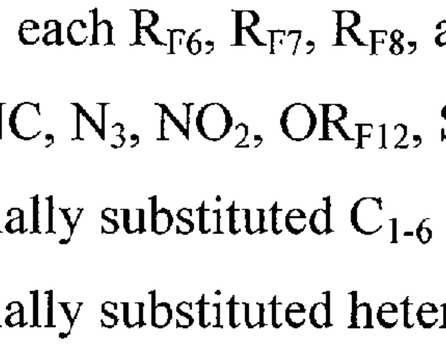
each R_{F3} and R_{F5} is selected, independently, from H, halogen, CN, CO_2R_{F12}, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{F6}, R_{F7}, R_{F8}, and R_{F9} is selected, independently, from H, halogen, CN, NC, N_3, NO_2, OR_{F12}, SR_{F12}, $NR_{F12}R_{F13}$, $-COR_{F12}$, $-CO_{2\,F12}$, $-CONR_{F12}R_{F13}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

where n is an integer between 1-6;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Certain compounds of Formula (VII) can also be described by Formula (VII-A)



(VII-A), where

Z_{F1} is selected from a single bond, -(CH_2)-, -C(=O)-, or -$S(=O)_2$-;

R_{F1} is selected from H, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R_{F2} and R_{F4} are each H, or R_{F2} and R_{F4} combine to form a carbon-carbon double bond;

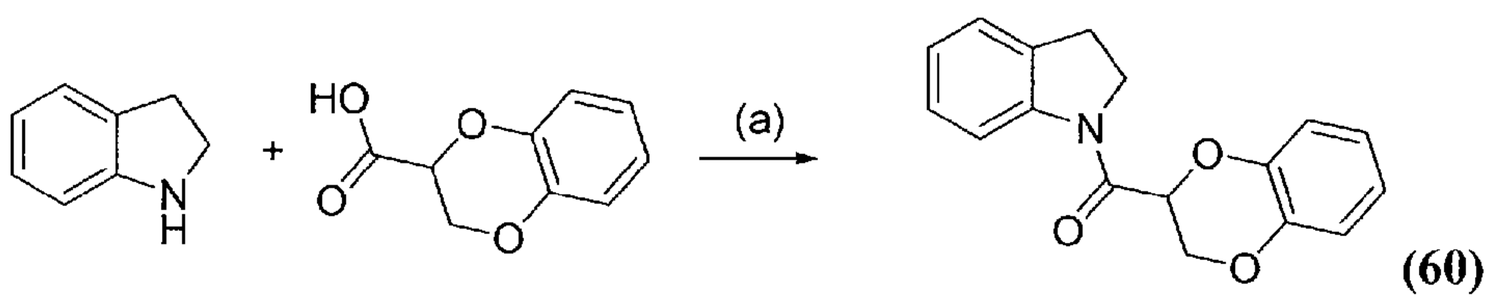
each R_{F6}, R_{F7}, R_{F8}, and R_{F9} is selected, independently, from H, halogen, CN, NC, N_3, NO_2, OR_{F12}, SR_{F12}, $NR_{F12}R_{F13}$, -COR_{F12}, -CO_2F12, -$CONR_{F12}R_{F13}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R_{F12} and R_{F13}, is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (VII-A), when R_{F2}, R_{F4}, R_{F6}, R_{F7}, R_{F8}, and R_{F9} are each H and Z_{F1} is -C(=O)-, R_{F1} is not - (unsubstituted 1,4-benzodioxane) or -CH_2-(O-(unsubstituted phenyl)).

Scheme 10



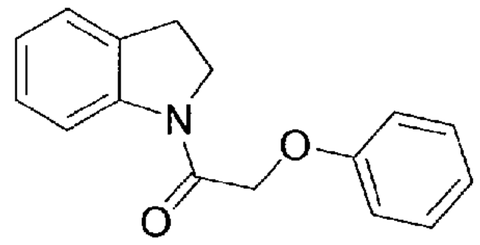
(60)

(a) Diethyl azodicarboxylate (DEAD), PPh_3, THF, rt.

Scheme 10 provides a method by which compounds of Formula (VII) such as **Compound (60)** can be prepared. For example, a nucleophilic compound such as indoline can be treated with an electrophile (e.g., a compound containing a carboxylic acid) in the presence of an optional

promoter such as DEAD/PPh_3 to afford the requisite compound. Another compound of Formula (VIII) is Compound **(61)** (**Scheme 11**).

Scheme 11

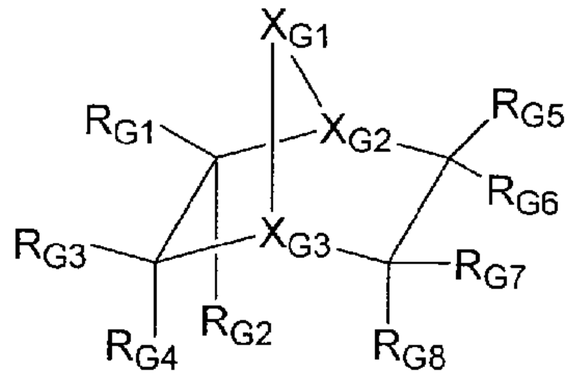


(61)

Compounds of Formula (VII) (e.g., (VII-A) and compound **(60)**), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits). In some embodiments, Formulas (VII) and (VII-A) do not include compounds **(60)** or **(61)**.

Compounds of Formula (VIII)

Still other compounds useful in the invention are described by Formula (VIII):



(VIII), where

X_{G1} is selected from -O-, -N-, or $-(CR_{G9}R_{G10})_n-$;

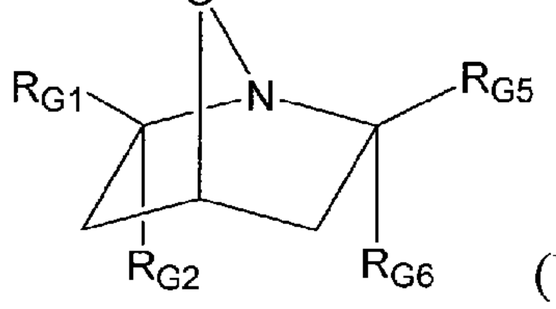
X_{G2} and X_{G3} are selected, independently, from N or CR_{G11};

each R_{G1}, R_{G2}, R_{G3}, R_{G4}, R_{G5}, R_{G6}, R_{G7}, R_{G8}, R_{G9}, R_{G10}, and R_{G11} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{G1} and R_{G2}, or R_{G3} and R_{G4}, or R_{G5} and R_{G6}, or R_{G7} and R_{G8} combine to form an optionally substituted cycloalkyl or heterocyclyl; and

n is 1 or 2;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Select compounds of Formula (VIII) can also be described by Formula (VIII-A):



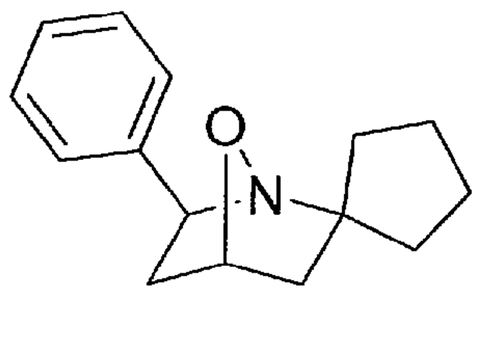
(VIII-A), wherein each R_{G1}, R_{G2}, R_{G5}, and R_{G6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{G1} and R_{G2}, or R_{G5} and R_{G6} combine to form an optionally substituted cycloalkyl or heterocyclyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

In some embodiments of Formula (VIII-A), when R_{G1} is unsubstituted phenyl and R_{G2} is H, R_{G5} and R_{G6} do not combine to form unsubstituted cyclopentyl,

Methods by which compounds of Formula (VIII) (e.g., compounds of Formula (VIII-A) can be prepared are known in the art. For example, **Compound (62)** shown in **Scheme 12**, can be prepared according to methods described in *Synthesis*, pages 771-783 (2002).

Scheme 12



(62)

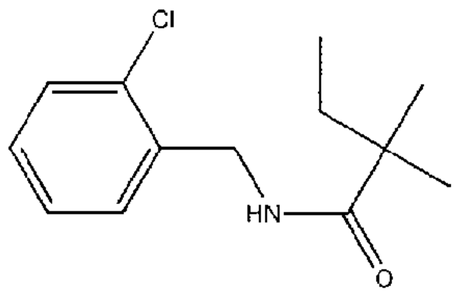
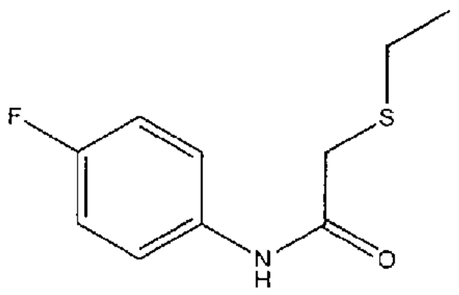
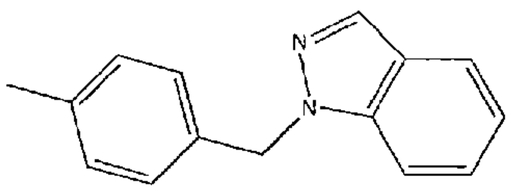
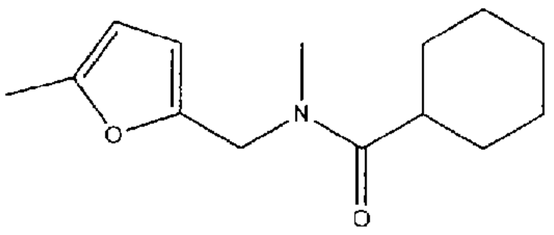
Compounds of Formula (VIII) (e.g., (VIII-A) and compound (**62**)), or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof, can also be used as described herein (e.g., in pharmaceutical compositions, as inhibitors of necroptosis, in methods of treatment, and in kits).

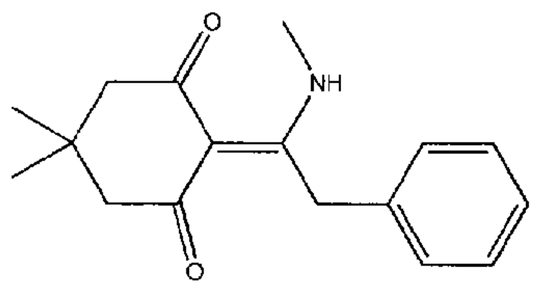
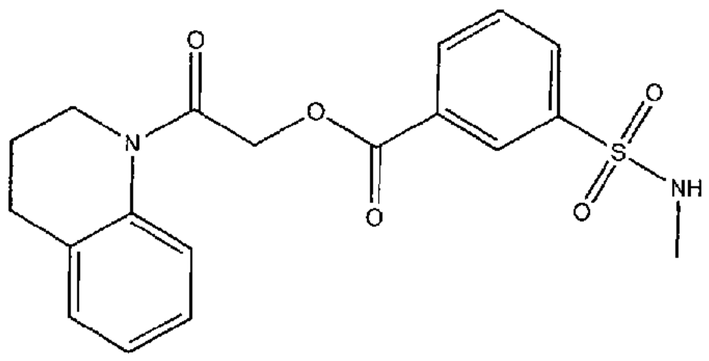
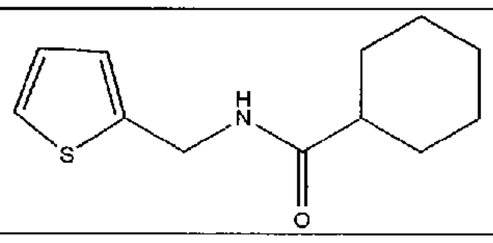
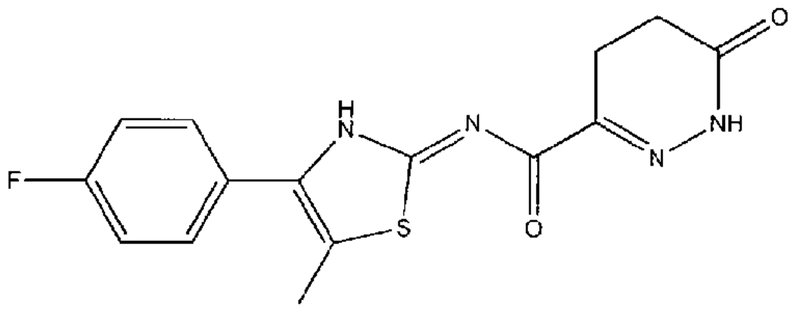
In some embodiments, Formulas (VIII) and (VIII-A) do not include compound **(62)**.

Additional Inhibitors of Necroptosis

Other compounds useful in the compositions, kits, and methods of the invention are described in U.S. Patent Nos. 6,756,394 and 7,253,201, in U.S. Patent Publication No. 20050119260, and in pending U.S. Application Nos. 12/077,320 and 12/086,792, each of which is hereby incroporated by reference. In addition to the compounds described by Formulas (I)-(VIII), other inhibitors of necroptosis include, but are not limited to, the structures depicted in **Table 8**, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

Table 8

Compound	Structure
(63)	
(64)	
(65)	
(66)	

Compound	Structure
(67)	
(68)	
(69)	
(70)	

Pharmaceutical Compositions

The necrostatins described herein (e.g., compounds of Formulas (I)-(VIII) or any of compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), or (58)-(70)) can be formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration in vivo. Accordingly, the present invention provides a pharmaceutical composition comprising a compound of the invention in admixture with a pharmaceutically acceptable excipient. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19), published in 1999.

The compounds may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the scope of the invention. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the invention may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

Pharmaceutically Acceptable Excipients

Pharmaceutically acceptable excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

Oral Administration

Any of the compounds described herein (e.g., compounds of Formulas (I)-(VIII) or any of compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), or (58)-(70)) may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound of the invention may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Parenteral Administration

A compound may also be administered parenterally. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe.

Nasal Administration

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as

compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

Buccal or Sublingual Administration

Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter.

The compounds of the invention may be administered to an animal alone or in combination with pharmaceutically acceptable carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosage Amounts

The amount of active ingredient (e.g., a compound of Formulas (I)-(VIII) or any of compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), or (58)-(70)) in the compositions of the invention can be varied. One skilled in the art will appreciate that the exact individual dosages may be adjusted somewhat depending upon a variety of factors, including the protein being administered, the time of administration, the route of administration, the nature of the formulation, the rate of excretion, the nature of the subject's conditions, and the age, weight, health, and gender of the patient. Generally, dosage levels of between 0.1 μg/kg to 100 mg/kg of body weight are administered daily as a single dose or divided into multiple doses. Desirably, the general dosage range is between 250 μg/kg to 5.0 mg/kg of body weight per day. Wide variations in the needed dosage are to be expected in view of the differing efficiencies of the various routes of administration. For instance, oral administration generally would be expected to require higher dosage levels than administration by intravenous injection. Variations in these dosage levels can be adjusted using

standard empirical routines for optimization, which are well known in the art. In general, the precise therapeutically effective dosage will be determined by the attending physician in consideration of the above identified factors.

Therapeutic Uses and Screening Methods

The compounds disclosed herein (e.g., compounds of Formulas (I)-(VIII) or any of compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), or (58)-(70)) can be used to treat disorders where necroptosis is likely to play a substantial role (e.g., cerebral ischemia, traumatic brain injury, a neurodegenerative disease of the central or peripheral nervous system, the result of retinal neuronal cell death, the result of cell death of cardiac muscle, the result of cell death of cells of the immune system; stroke, liver disease, pancreatic disease, the result of cell death associated with renal failure; heart, mesenteric, retinal, hepatic or brain ischemic injury, ischemic injury during organ storage, head trauma, septic shock, coronary heart disease, cardiomyopathy, myocardial infarction, bone avascular necrosis, sickle cell disease, muscle wasting, gastrointestinal disease, tuberculosis, diabetes, alteration of blood vessels, muscular dystrophy, graft-versus-host disease, viral infection, Crohn's disease, ulcerative colitis, asthma, or any condition in which alteration in cell proliferation, differentiation or intracellular signaling is a causative factor). Compounds of the invention can also be used in screening methods to identify targets of necroptosis and to identify additional inhibitors of necroptosis, as well as in assay development.

Compounds disclosed herein can be evaluated for their pharmacological properties in animal models of disease. The compounds identified to decrease necrosis or necroptosis may be structurally modified and subsequently used to decrease necrosis or necroptosis, or to treat a subject with a condition in which necrosis or necroptosis occurs. The methods used to generate structural derivatives of the small molecules that decrease necrosis or necroptosis are readily known to those skilled in the fields of organic and medicinal chemistry.

Therapy according to the invention may be performed alone or in conjunction with another therapy, for example in combination with apoptosis inhibitors, and may be provided at homc, the doctor's office, a clinic, a hospital's outpatient department, or a hospital. Treatment generally begins at a hospital so that the doctor can observe the therapy's effects closely and make any adjustments that are needed. The duration of the therapy depends on the age and condition of the patient, as wcll as how the patient responds to the treatment. Additionally, a person having a greater risk of developing a condition may receive prophylactic treatment to inhibit or delay symptoms of the disease.

In some embodiments, the compounds and methods of the invention can be used to treat any of the following disorders where necroptosis is likely to play a substantial role: a neurodegenerative disease of the central or peripheral nervous system, the result of retinal neuronal cell death, the result of cell death of cardiac muscle, the result of cell death of cells of the immune system; stroke, liver disease, pancreatic disease, the result of cell death associated with renal failure; heart, mesenteric, retinal, hepatic or brain ischemic injury, ischemic injury during organ storagc, head trauma, septic shock, coronary heart disease, cardiomyopathy, myocardial infarction, bone avascular necrosis, sickle cell disease, muscle wasting, gastrointestinal disease, tuberculosis, diabetes, alteration of blood vessels, muscular dystrophy, graft-versus-host disease, viral infection, Crohn's disease, ulcerative colitis, asthma, and any condition in which alteration in cell proliferation, differentiation or intracellular signaling is a causative factor.

Conditions Caused by Alteration in Cell Proliferation, Differentiation, or Intracellular Signalling

Conditions in which alteration in cell proliferation, differentiation or intracellular signaling is a causative factor include cancer and infection, e.g., by viruses (e.g., acute, latent and persistent), bacteria, fungi, or other microbes.

Exemplary viruses are human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV)5 human herpesviruses (HHV), herpes simplex viruses (HSV), human T-Cell leukemia viruses (HTLV)5 Varicella-Zoster virus (VZV), measles virus, papovaviruses (JC and BK), hepatitis viruses, adenovirus, parvoviruses, and human papillomaviruses. Exemplary diseases caused by viral infection include, but are not limited to, chicken pox, Cytomegalovirus infections, genital herpes, Hepatitis B and C, influenza, and shingles.

Exemplary bacteria include, but are not limited to Campylobacter jejuni, Enterobacter species, Enterococcus faecium, Enterococcus faecalis, Escherichia coli (e.g., E. coli O157:H7), Group A streptococci, Haemophilus influenzae, Helicobacter pylori, listeria, Mycobacterium tuberculosis, Pseudomonas aeruginosa, S. pneumoniae, Salmonella, Shigella, Staphylococcus aureus, and Staphylococcus epidermidis. Exemplary diseases caused by bacterial infection include, but are not limited to, anthrax, cholera, diphtheria, foodborne illnesses, leprosy, meningitis, peptic ulcer disease, pneumonia, sepsis, tetanus, tuberculosis, typhoid fever, and urinary tract infection.

Neurodegenerative Diseases

Exemplary neurodegenerative diseases are Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, HIV-associated dementia, cerebral ischemia, amyotropic lateral sclerosis, multiple sclerosis, Lewy body disease, Menke's disease, Wilson's disease, Creutzfeldt-Jakob disease, and Fahr disease. Exemplary muscular dystrophies or related diseases are Becker's muscular dystrophy, Duchenne muscular dystrophy, myotonic dystrophy, limb-girdle muscular dystrophy, Landouzy-Dejerine muscular dystrophy, facioscapulohumeral muscular dystrophy (Steinert's disease), myotonia congenita, Thomsen's disease, and Pompe's disease. Muscle wasting can be associated with cancer, AIDS, congestive heart failure, and chronic obstructive pulmonary disease, as well as include necrotizing myopathy of intensive care.

Compounds and methods of the invention can additionally be used to boost the immune system, whether or not the patient being treated has an immunocompromising condition. For example, the compounds described herein can be used in a method to strengthen the immune system during immunization, e.g., by functioning as an adjuvant, or by being combined with an adjuvant.

Kits

Any of the compounds or pharmaceutical compositions of the invention (e.g., those that include a compound of Formulas (I)-(VIII) or any of compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), or (58)-(70)) can be used together with a set of instructions, i.e., to form a kit. The kit may include instructions for use of the compounds of the invention in a screening method or as a therapy as described herein.

The following non-limiting examples are illustrative of the present invention.

EXAMPLES

EXAMPLE 1: DETERMINATION OF NECROPTOSIS INHIBITORY ACTIVITY

Evaluation of necroptosis inhibitory activity was performed using a FADD-deficient variant of human Jurkat T cells or with L929 cells treated with TNF-α as previously described (Degterev et al., *Nat. Chem. Biol.* 1:112 (2005) and Jagtap et al., *J. Med. Chem.* 50: 1886 (2007)). Utilizing these conditions the cells efficiently underwent necroptosis. For EC_{50} value determinations, cells were treated with 10 ng/mL of human TNF-α in the presence of increasing concentration of test compounds for 24 hours followed by ATP-based viability assessment.

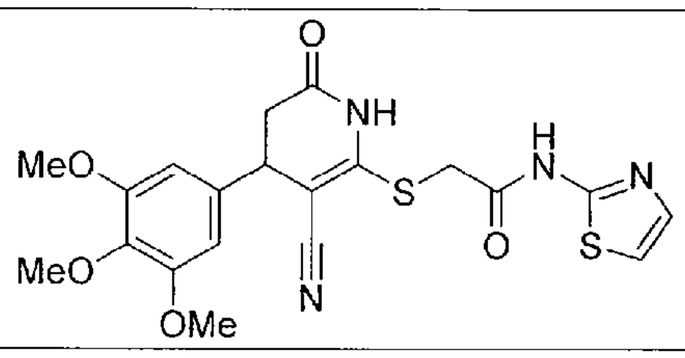
ATP-based viability assessment: Briefly, necroptosis activity was performed using a FADD-deficient variant of human Jurkat T cells or L929

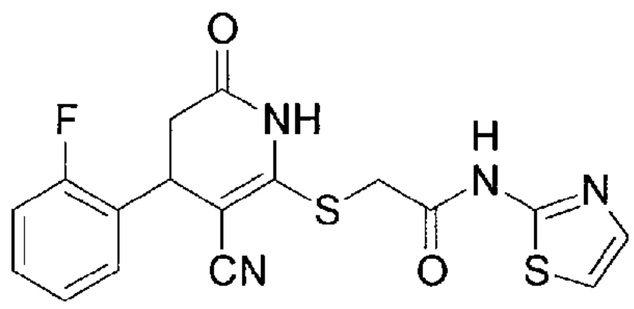
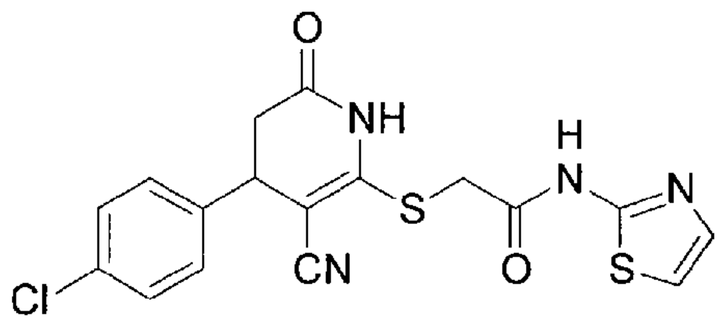
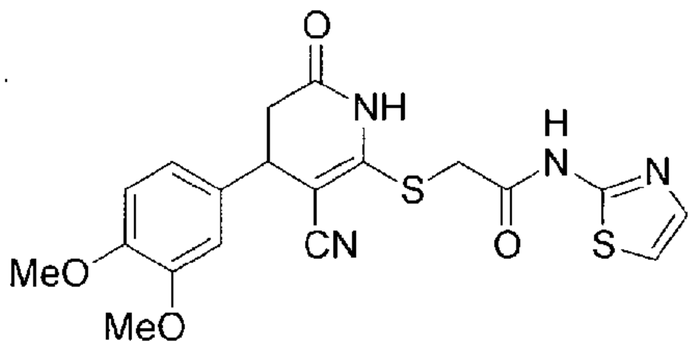
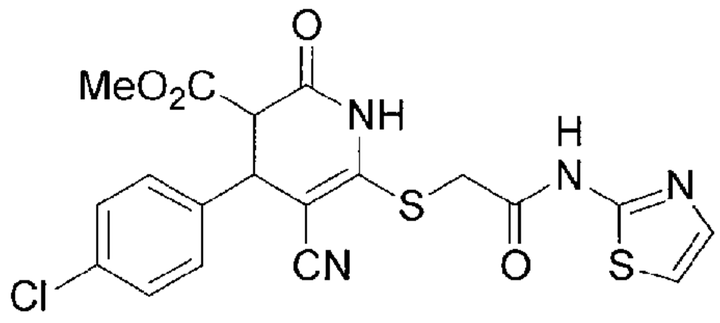
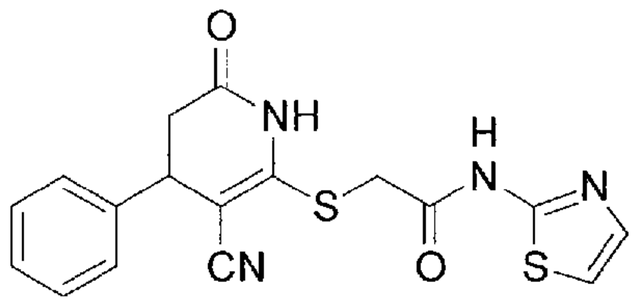
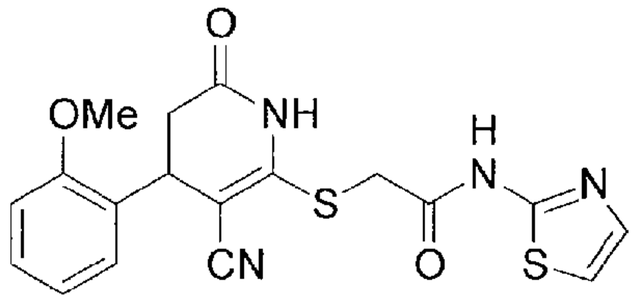
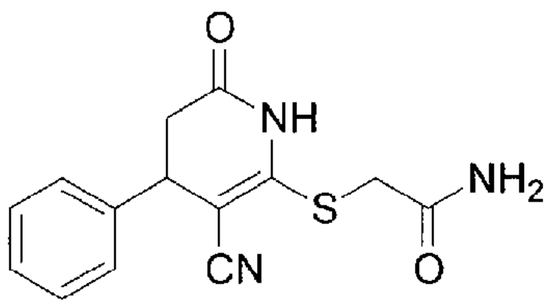
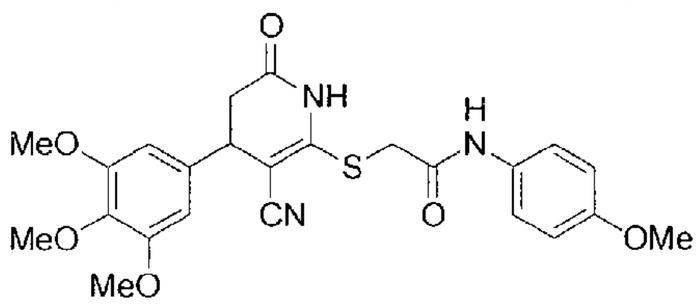
cells treated with TNF-α. For EC_{50} value determinations, cells (500,000 cells/mL, 100 μL per well in a 96-well plate) were treated with 10 ng/mL of human TNF-α in the presence of increasing concentration of test compounds for 24 hours at 37 °C in a humidified incubator with 5% CO_2 followed by ATP-based viability assessment. Stock solutions (30 mM) in DMSO were initially prepared and then diluted with DMSO to give testing solutions, which were added to each test well. The final DMSO concentration was 0.5%. Eleven compound test concentrations (0.030 – 100 μM) were used. Each concentration was done in duplicate.

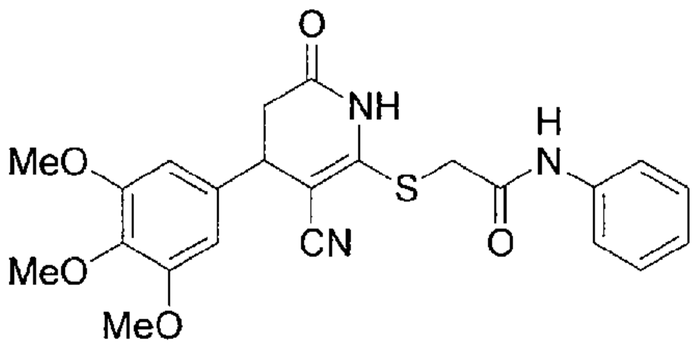
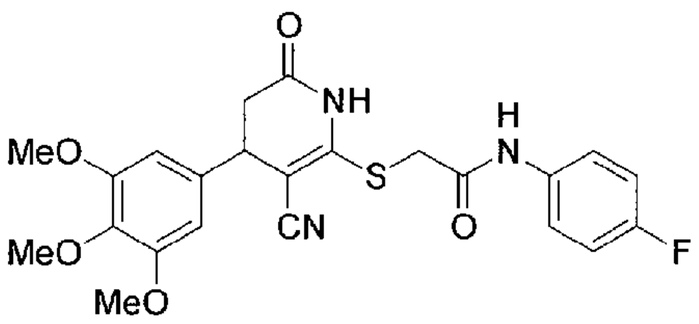
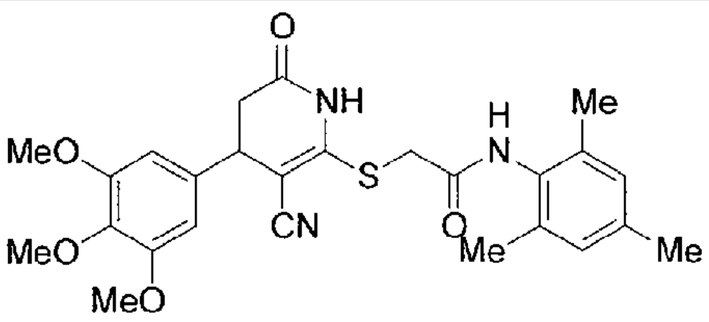
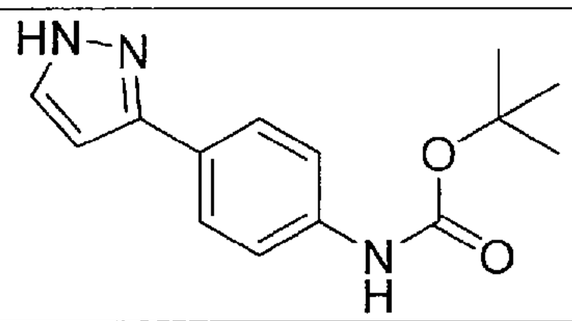
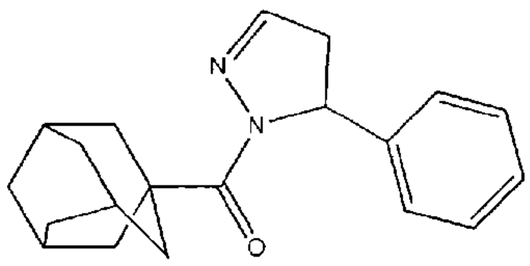
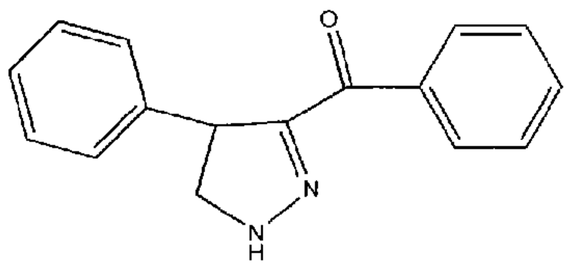
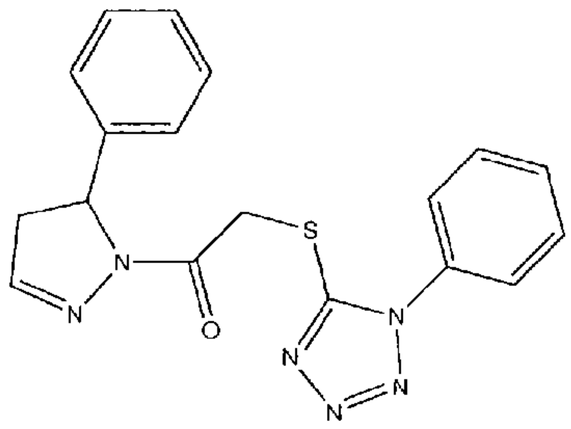
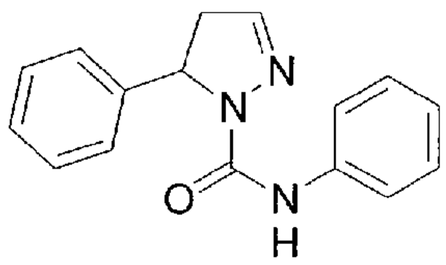
Cell viability assessments were performed using a commercial luminescent ATP-based assay kit (CellTiter-Glo, Promega, Madison, WI) according to the manufacturer's instructions. Briefly, 40 μL of the cell lysis/ATP detection reagent was added to each well. Plates were incubated on a rocking platform for 10 minutes at room temperature and luminescence was measured using a Wallac Victor 3 plate-reader (Perkin Elmer, Wellesley, MA). Cell viability was expressed as a ratio of the signal in the well treated with TNF-α and compound to the signal in the well treated with compound alone. This was done to account for nonspecific toxicity, which in most cases was < 10%. EC_{50} values were calculated using nonlinear regression analysis of sigmoid dose-response (variable slope) curves from plots of log[I] verses viability values.

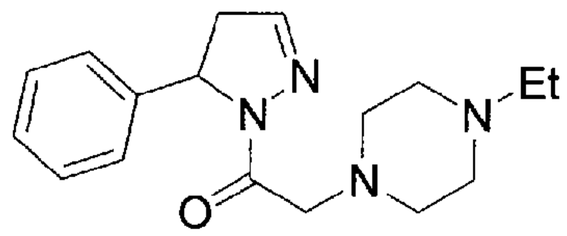
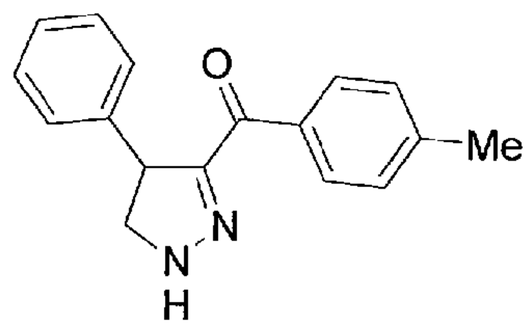
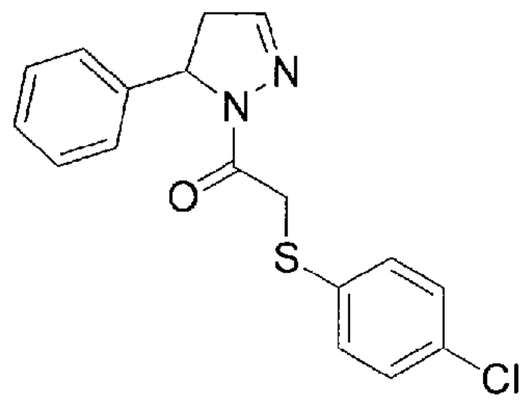
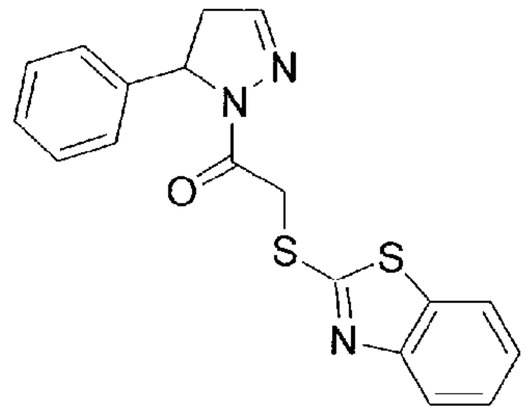
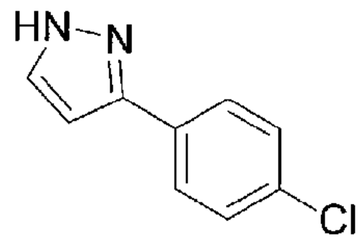
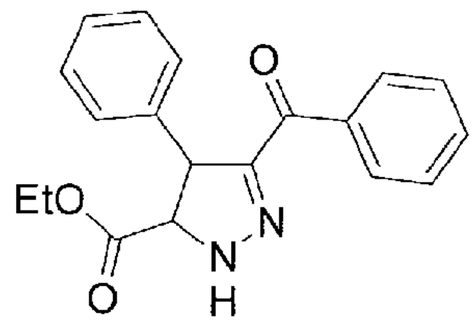
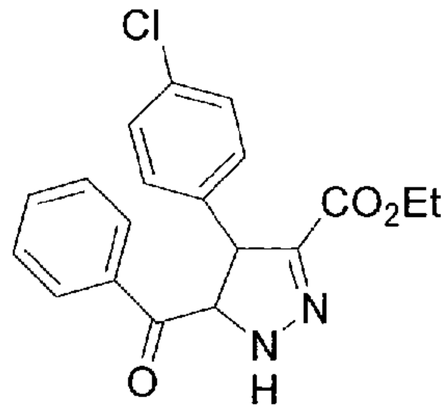
Results obtained using these procedures are shown in Table 9.

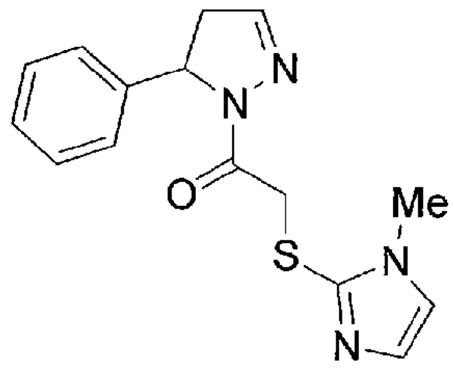
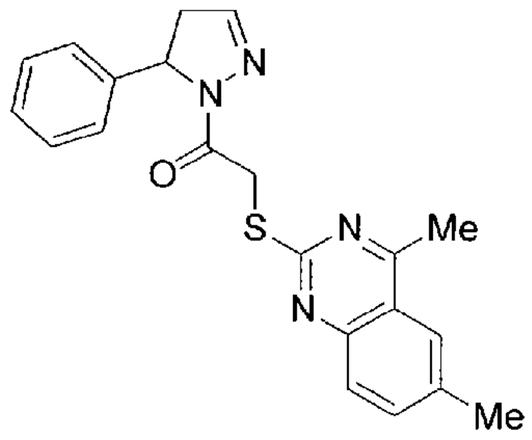
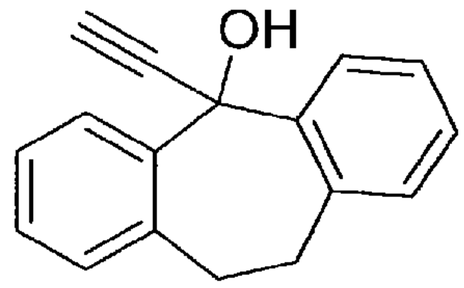
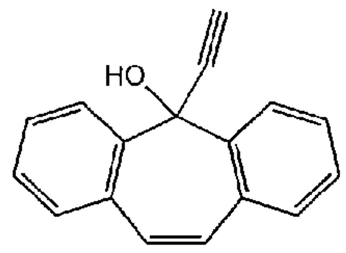
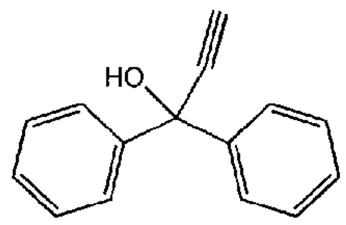
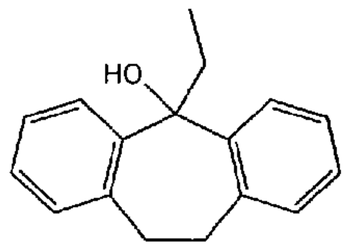
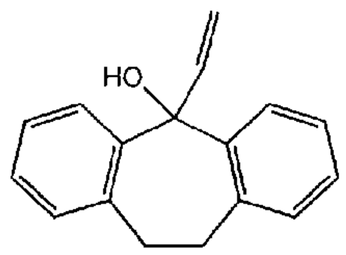
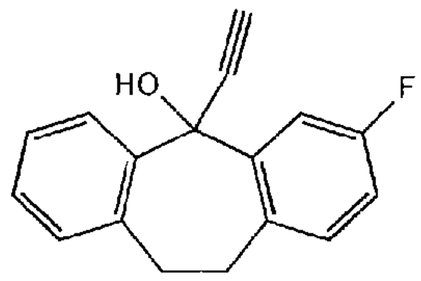
Table 9

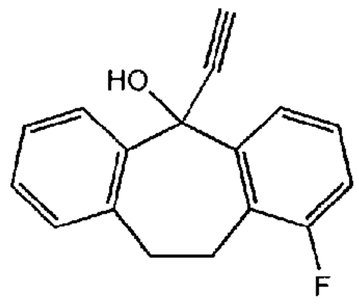
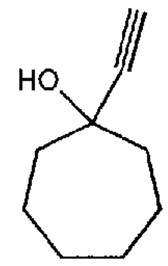
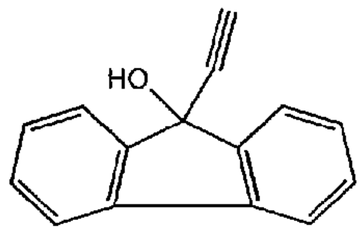
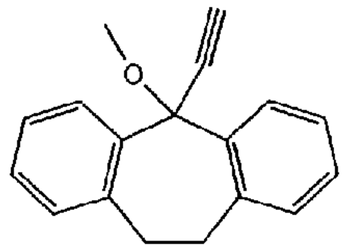
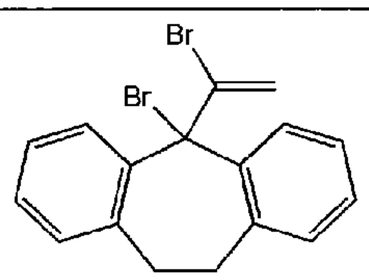
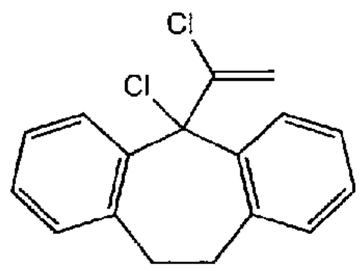
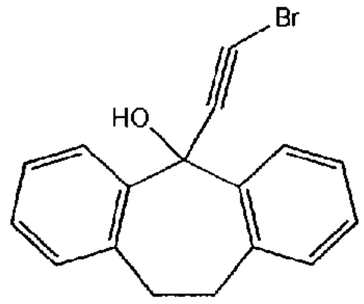
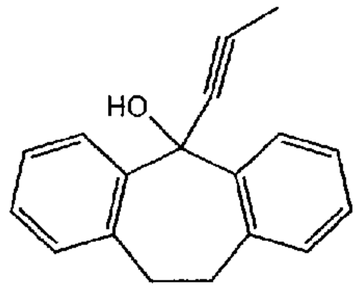
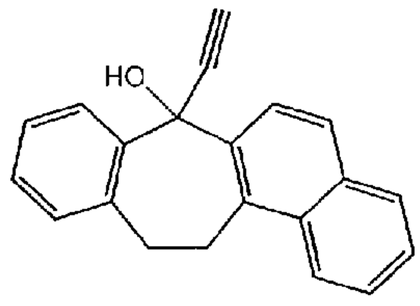
Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(1)		0.4769	0.1971	>2000

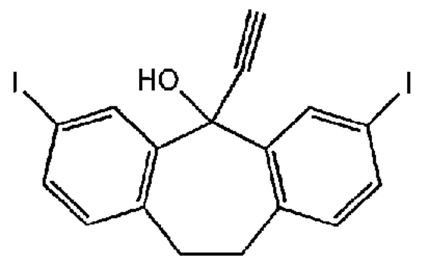
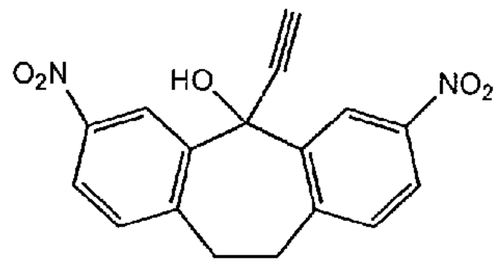
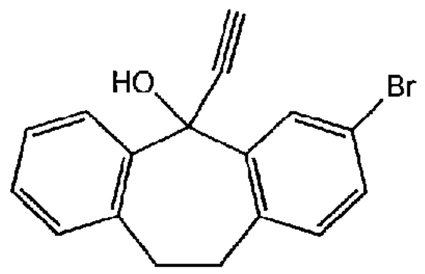
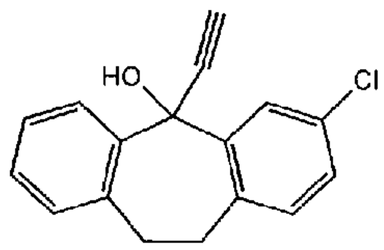
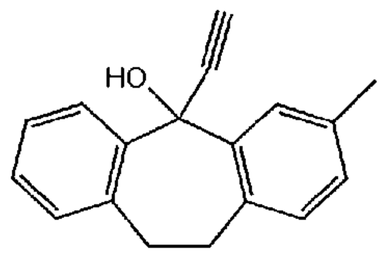
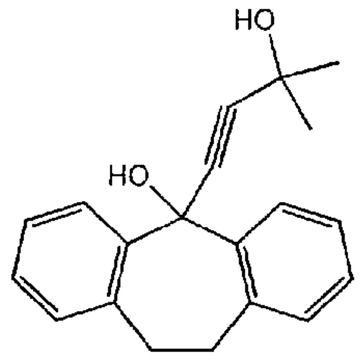
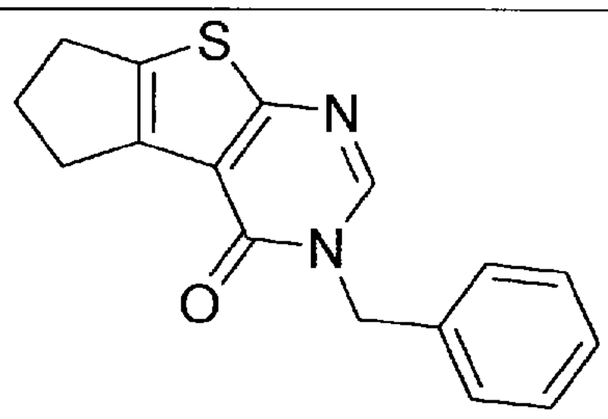
Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(2)		0.7690	--	--
(3)		0.8232	--	--
(4)		0.3540	--	--
(5)		24.98	--	--
(6)		Partial activity	--	--
(7)		2.379	--	--
(8)		inactive		
(9)		inactive		

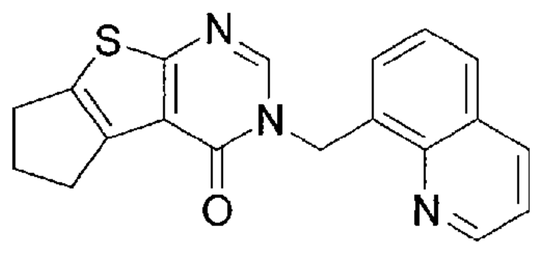
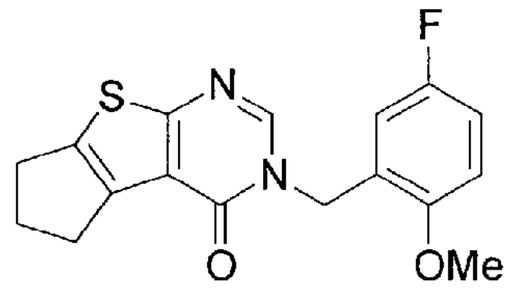
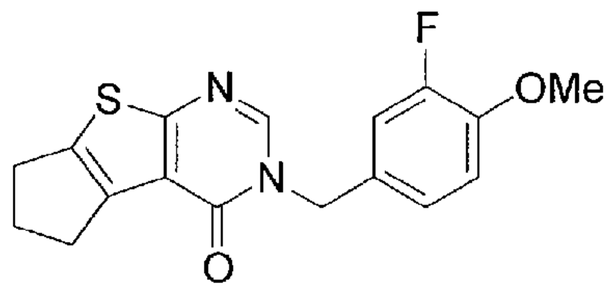
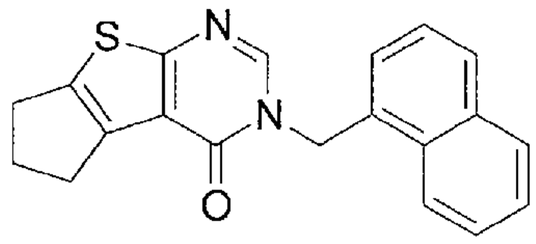
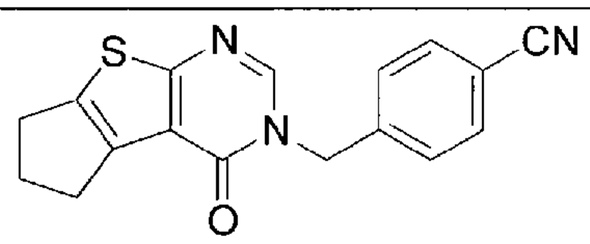
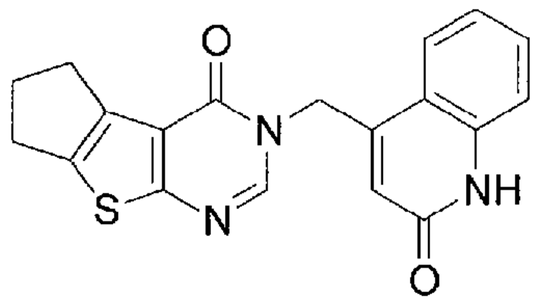
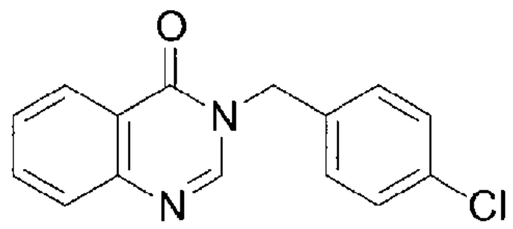
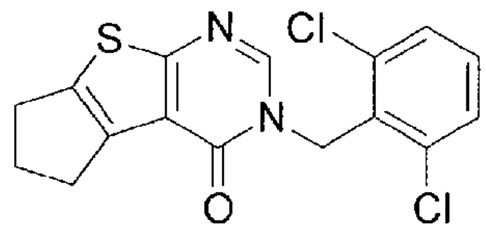
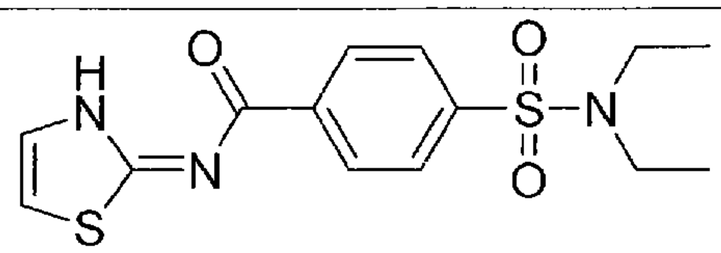
Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(10)		inactive		
(11)		inactive		
(12)		inactive		
(13)		5.379	0.89	539.4
(14)		0.4101	4.202	396.9
(15)		0.3688	4.02	799.5
(16)		0.6289	72.97	247.7
(17)		inconclusive	--	--

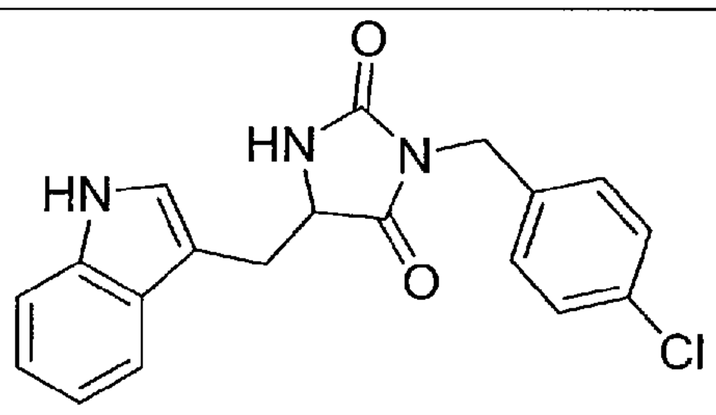
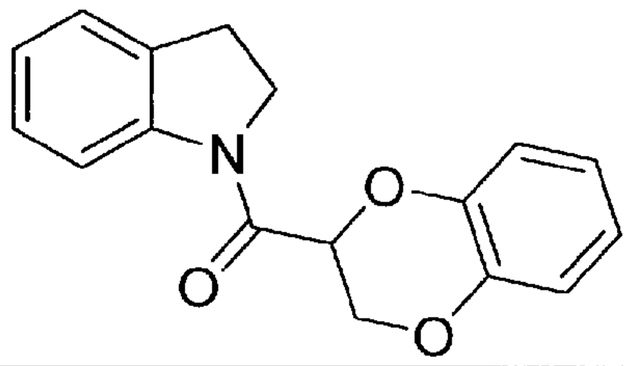
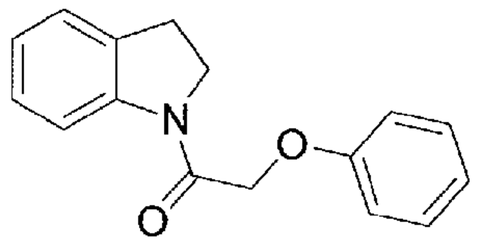
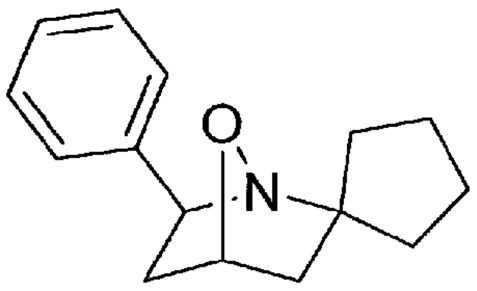
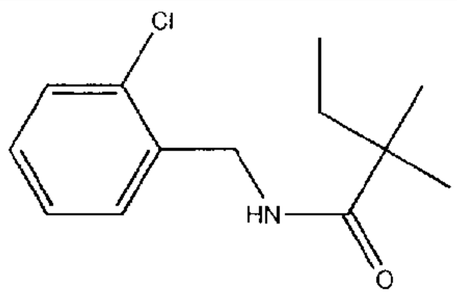
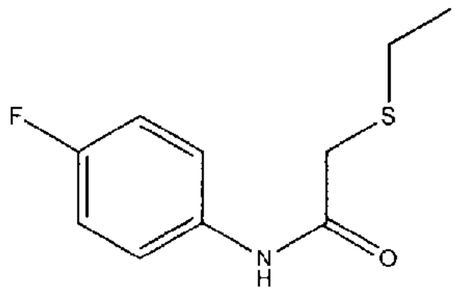
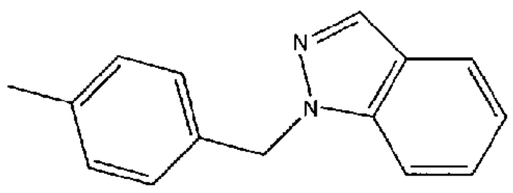
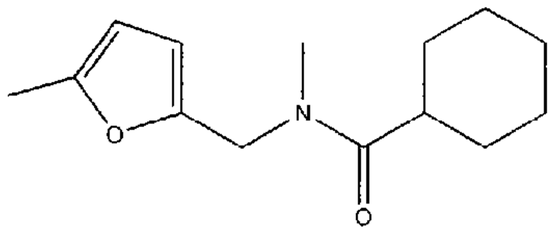
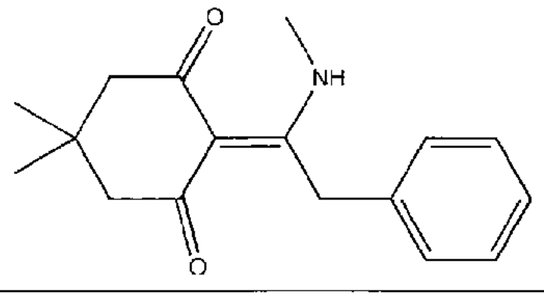
Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(18)		0.4101	--	--
(19)		0.3688	--	--
(20)		3.211	--	--
(21)		1.557	--	--
(22)		Inactive		
(23)		Inactive		
(24)		Inactive		

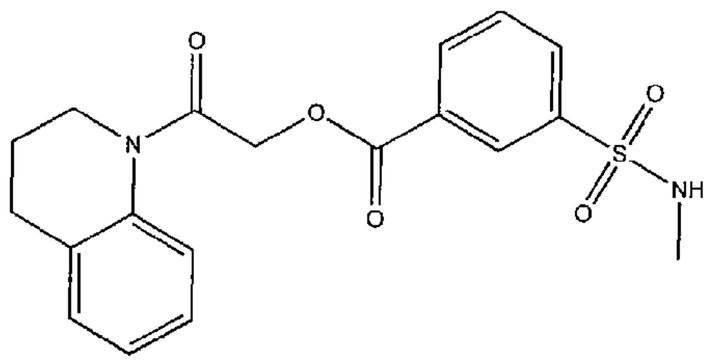
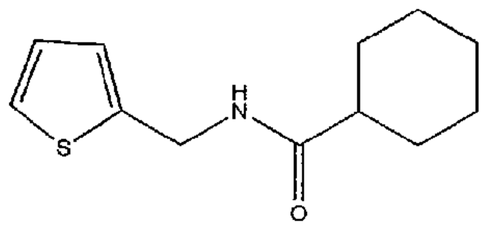
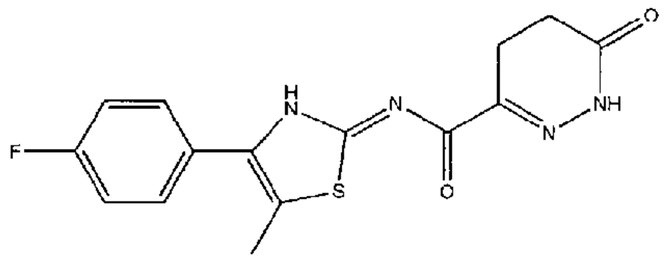
Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(25)		Inactive		
(26)		Inactive		
(27)		3.227	0.659	541.3
(28)		2.98	--	--
(29)		31.78	--	--
(30)		5.833	--	--
(31)		2.954	--	--
(32)		2.002	--	--

Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(33)		4.788	--	--
(34)		Inactive		
(35)		Inactive		
(36)		Inactive		
(37)		Inactive		
(38)		Inactive		
(39)		Inactive		
(40)		Inactive		
(41)		Inactive		

Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(42)		Inactive		
(43)		Inactive		
(44)		Inactive		
(45)		Inactive		
(46)		Inactive		
(47)		Inactive		
(48)		0.2161	8.66	188.9
(49)		3.803	--	--

Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(50)		>30	--	--
(51)		10.88	--	--
(52)		3.046	--	--
(53)		>30	--	--
(54)		0.8606	--	--
(55)		>30	--	--
(56)		>30	--	--
(57)		0.9363	--	--
(58)		8.958	1.11	>2000

Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(59)		0.3431	7.458	115.7
(60)		0.6289	23.04	356.5
(61)		Inactive		
(62)		0.6683	10.09	754
(63)		2.364	13.7	1364
(64)		14.14	Inactive	1788
(65)		3.621	Inactive	138.6
(66)		2.616	47.12	256.8
(67)		2.245	10.02	697.8

Compound no.	Structure	EC_{50} Fadd -/- Jurkat	EC_{50} L929	LD_{50} Fadd -/- Jurkat
(68)		1.633	Inactive	252.3
(69)		7.724	Inactive	1571
(70)		0.9077	Inactive	>2000

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

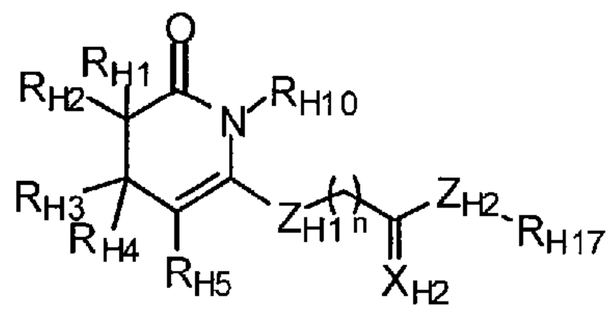
While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are within the claims.

What is claimed is:

CLAIMS

1. A compound having a structure according to the following formula



(I-A), wherein

each R_{H1}, R_{H2}, R_{H3}, R_{H4}, R_{H5}, R_{H10}, R_{H17}, X_{H2}, Z_{H1}, Z_{H2}, and n is as defined for Formula (I),

X_{H2} is selected, independently, from O, S, or NR_{H9};

each R_{H1}, R_{H2}, R_{H3}, R_{H4}, and R_{H5} is selected, independently from H, halogen, cyano, nitro, azido, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(=O)R_{H12}$, $-C(=O)OR_{H12}$, $-C(=O)NR_{H12}R_{H13}$, $-C(=S)R_{H12}$, $-C(=S)NR_{H12}R_{H13}$, $-C(=NR_{H14})R_{H12}$, $-C(=NR_{H14})NR_{H12}R_{H13}$, or $-[Z_{H1}-(CR_{H15}R_{H16})_n-\{C(=X_{H2})\}_o-Z_{H2}-R_{17}]$, or R_{H1} and R_{H3} combine to form a carbon-carbon double bond;

each Z_{H1} and Z_{H2} is selected, independently, from a single bond, O, S, or NR_{H11};

each R_{H9}, R_{H10}, R_{H11}, R_{H12}, R_{H13}, R_{H14}, R_{H15}, R_{H16}, and R_{H17}, is selected, independently from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

n is an integer between 0-6; and

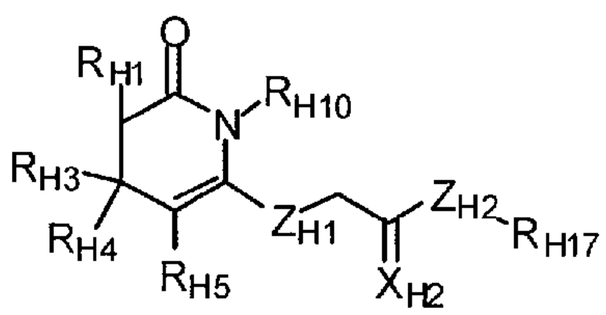
o is 0 or 1; and

wherein when R_{H1} is H, R_{H2} is H or CO_2Me, R_{H3} is H, R_{H4} is unsubstituted phenyl or phenyl substituted with 1, 2, or 3 substituents selected from methoxy, methyl, chloro, or fluoro, R_{H5} is CN, R_{H10} is H, Z_{H1} is S, n is 1, X_{H2} is O, and Z_{H2} is NH, R_{H17} is not H, methoxy, unsubstituted 2-thiazolyl,

unsubstituted phenyl, 4-methoxyphenyl, 4-methylphenyl, 2-ethoxyphenyl, 4-isopropylphenyl, 4-fluorophenyl, or 2,4,6-trimethylphenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

2. The compound of claim 1, wherein said compound has a structure according to Formula (I-B)



(I-B), wherein

each R_{H1} and R_{H3} is selected, independently, from H, halogen, cyano, nitro, azido, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(=O)R_{H12}$, $-C(=O)OR_{H12}$, or $-C(=O)NR_{H12}R_{H13}$, or R_{H1} and R_{H3} combine to form a carbon-carbon double bond;

each R_{H4} and R_{H17} is selected, independently, from optionally substituted aryl or optionally substituted heteroaryl;

R_{H5} is selected from H, CN, $-C(=O)OR_{H12}$, or $-C(=O)NR_{H12}R_{H13}$;

each R_{H10}, R_{H11}, R_{H12}, and R_{H13} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

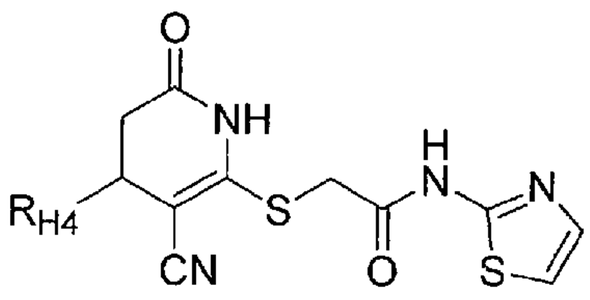
Z_{H1} is selected from a single bond or S;

Z_{H2} is selected from a single bond or NR_{H11}; and

X_{H2} is O or S;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

3 The compound of claim 2, wherein said compound has the following structure



(I-C),

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

4. The compound of claim 2, wherein R_{H1} and R_{H3} are H,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

5. The compound of claim 2, wherein R_{H5} is CN,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

6. The compound of claim 2, wherein R_{H10} is H,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

7. The compound of claim 2, wherein Z_{H1} is S,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

8. The compound of claim 2, wherein Z_{H2} is NH,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

9. The compound of claim 2, wherein R_{H4} is unsubstituted phenyl or phenyl having 1, 2, 3, 4, or 5 substituents,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

10. The compound of claim 9, wherein said phenyl comprises 1, 2, or 3 substituents selected from F, Cl, or OR_{H18}, wherein each R_{H18} is, independently, selected from H or optionally substituted C_{1-6} alkyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

11. The compound of claim 10, wherein said phenyl is 2-fluorophenyl, 2-chlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3, 4, 5-trimethoxyphenyl, or 3, 4-dimethoxyphenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

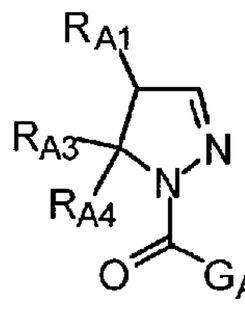
12. The compound of claim 2, wherein R_{H17} is optionally substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

13. The compound of claim 12, wherein said heteroaryl selected from furan, thiophene, pyrrole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,3-oxadiazole or 1,2,5-oxadiazole, oxazole, benzoxazole, isoxazole, isothiazole, pyrazole, thiazole, benzthiazole, 1,2,4-triazole, 1,2,3-triazole, benzotriazole, pyridine, pyrimidine, pyrazines, quinoline, isoquinoline, purine, pyrazine, pteridine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, indole, 1,2,4,5-tetrazine, benzo[*b*]thiophene, benzo[*c*]thiophene, benzofuran, isobenzofuran, and benzimidazole,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

14. A compound having a structure according to the following formula



(II-A), wherein

each R_{A1}, R_{A3}, and R_{A4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

G_{A2} is absent or -$(CR_{A11}R_{A12})_n$-;

X_{A3} is absent or is O, S, or NR_{A8};

each R_{A8} and R_{A13} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -COR_{A14}, -CO_2R_{A14}, or -$CONR_{A14}R_{A15}$;

each R_{A9}, R_{A10}, R_{A11}, and R_{A12} is selected, independently, from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{A7}, R_{A14} and R_{A15} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl; and

each m and n is, independently, 1, 2, or 3; and

wherein when one of R_{A1} and R_{A4} is H and the other is selected from H or CO_2Et, and R_{A3} is unsubstituted phenyl, G_{A2}-X_{A3}-R_{A7} is not NHC_6H_5, NH(p-

C_6H_4F), NH(p-C_6H_4OH), NH(p-C_6H_4OMe), NH(3-OH-4-Cl-C_6H_4), -CH_2(O-*p*-C_6H_4Me), -CH_2(4-ethylpiperazinyl), -CH_2S(2-phenyltetrazolyl), -CH_2S(4-chlorophenyl), -CH_2S(2-benzothiazolyl), -CH_2S(2-(N-methylimidazolyl)), -CH_2S(4,6-dimethylquinazolinyl), adamantyl, or optionally substituted oxiranyl; and

wherein when R_{A1} and R_{A4} are each H and R_{A3} is 4-methoxyphenyl, G_{A2}-X_{A3}-R_{A7} is not optionally substituted oxiranyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

15. The compound of claim 14, wherein R_{A1} and R_{A4} are H,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

16. The compound of claim 14, wherein R_{A3} is unsubstituted phenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

17. The compound of claim 14, wherein R_{A3} is phenyl having 1, 2, 3, 4, or 5 substituents,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

18. The compound of claim 16, wherein G_{A2} is absent,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

19. The compound of claim 18, wherein X_{A3} is absent and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

20. The compound of claim 19, wherein X_{A3} is NR_{A8} and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

21. The compound of claim 14, wherein G_{A2} is CH_2,
or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

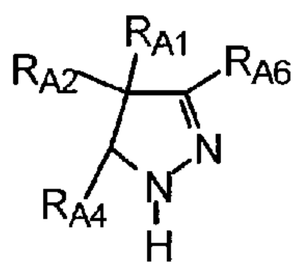
22. The compound of claim 21, wherein X_{A3} is S and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

23. The compound of claim 20, wherein X_{A3} is absent and R_{A7} is optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

24. A compound having a structure according to the following formula



(II-C), wherein

each R_{A1}, R_{A2}, R_{A4}, and R_{A6} is selected, independently, from H, -C(=O)-X_{A3}-R_{A7}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

each X_{A3} is, independently, absent, -O-, or -NR_{A8}-,

each R_{A8} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -COR_{A14}, -CO_2R_{A14}, or -$CONR_{A14}R_{A15}$;

each R_{A7}, R_{A14} and R_{A15} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl; and

wherein when R_{A1} and R_{A4} combine to form a carbon-carbon double bond and R_{A2} is H, R_{A6} is not 4-chlorophenyl, 4-methoxyphenyl, or 4-($NHCO_2{}^tBu$)phenyl;

wherein when R_{A1} is H, R_{A4} is H or CO_2Et, R_{A2} is unsubstituted phenyl, R_{A6} is not –C(=O)-(unsubstituted phenyl) or –C(=O)-(4-methylphenyl); and

wherein when R_{A1} is H, R_{A4} is –C(=O)-(unsubstituted phenyl), R_{A2} is 4-chlorophenyl, R_{A6} is not CO_2Et;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

25. The compound of claim 24, wherein

R_{A5} is H;

each R_{A1}, R_{A2}, R_{A4}, and R_{A6} is selected, independently, from H, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)-X_{A3}-R_{A7}, or R_{A1} and R_{A4} combine to form a carbon-carbon double bond;

each R_{A7} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each X_{A3} is, independently, absent, -O-, or -NR_{A8}-,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

26. The compound of claim 24, wherein R_{A1} and R_{A4} combine to form a carbon-carbon double bond,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

27. The compound of claim 26, wherein R_{A6} is optionally substituted aryl or optionally substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

28. The compound of claim 27, wherein R_{A6} is a phenyl group having a substituent at the 4-position,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

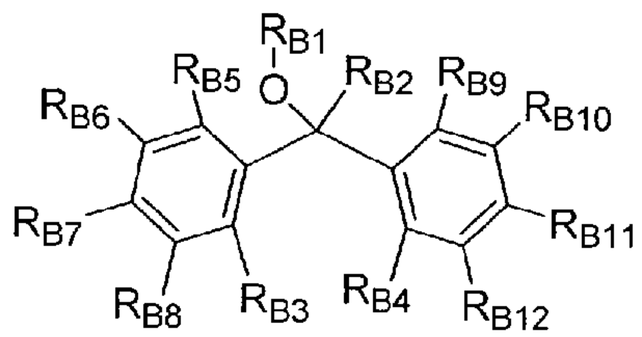
29. The compound of claim 24, wherein R_{A1} and R_{A4} are each H, R_{A2} is optionally substituted aryl or optionally substituted heteroaryl, and R_{A6} is $-C(=O)-X_{A3}-R_{A7}$,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

30. The compound of claim 29, wherein R_{A2} is unsubstituted phenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

31. A compound having a structure according to the following formula



(III), wherein

R_{B1} is selected from H, optionally substituted C_{1-6} alkyl, $-C(=O)R_{B18}$, $-C(=O)OR_{B18}$, or $-C(=O)NR_{B18}R_{B19}$;

R_{B2} is selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R_{B3} and R_{B4} is selected, independently from H, optionally substituted C_{1-6} alkyl, or R_{B3} and R_{B4} combine to form a bridging group having the structure $-(CH_2)_n-(CR_{B13}=CR_{B14})_o-(CH_2)_p-$;

each n, o, and p is, independently, 0 or 1;

each R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H, halogen, –CN, $-NO_2$, $-N_3$, $-R_{B13}$, $-OR_{B13}$, $-SR_{B13}$, $-NR_{B13}R_{B14}$, $-C(=O)R_{B15}$, $-C(=O)OR_{B15}$, $-C(=O)NR_{B15}R_{B16}$, $-OC(=O)R_{B15}$, $-OC(=O)OR_{B15}$, $-OC(=O)NR_{B15}R_{B16}$, $-NR_{B15}C(=O)R_{B15}$, $-NR_{B15}C(=O)OR_{B16}$, $-NR_{B15}C(=O)NR_{B16}R_{B17}$, $-C(=S)R_{B15}$, $-C(=S)NR_{B15}R_{B16}$, $-NR_{B15}C(=S)R_{B16}$, $-NR_{B15}C(=S)NR_{B16}R_{B17}$, $-C(=NR_{B13})NR_{B15}R_{B16}$, $-NR_{B15}C(=NR_{B13})R_{B16}$, $-NR_{B15}C(=NR_{B13})NR_{B16}R_{B17}$;

each R_{B13} and R_{B14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R_{B18}$, $-C(=O)OR_{B18}$, or $-C(=O)NR_{B18}R_{B19}$,

each R_{B15}, R_{B16}, R_{B17}, R_{B18}, and R_{B19} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

wherein when each n, o, and p is 0, R_{B3} and R_{B4} combine to form a single bond, and

wherein R_{B1} is not H or CH_3 when R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B9}, R_{B10}, R_{B11}, and R_{B12} are each H, R_{B2} is ethyl, ethenyl, 2-haloethenyl, ethynyl, haloethynyl, propynyl, or $-C\equiv C-C(OH)(CH_3)_2$, and when R_{B3} and R_{B4} are each H or combine to form a bond, $-CH_2CH_2-$ or $-CH=CH-$;

wherein R_{B1} is not H when R_{B5}, R_{B6}, R_{B7}, R_{B8}, R_{B10}, and R_{B11} are each H, at least one of R_{B9} or R_{B12} is fluoro, R_{B2} is ethynyl, and when R_{B3} and R_{B4} combine to form $-CH_2CH_2-$;

wherein R_{B1} is not H when R_{B5}, R_{B7}, R_{B9}, and R_{B11} are H and one or two of R_{B6}, R_{B8}, R_{B10}, and R_{B12} is halogen, nitro, or methyl; and

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

32. The compound of claim 31, wherein R_{B1} is H, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

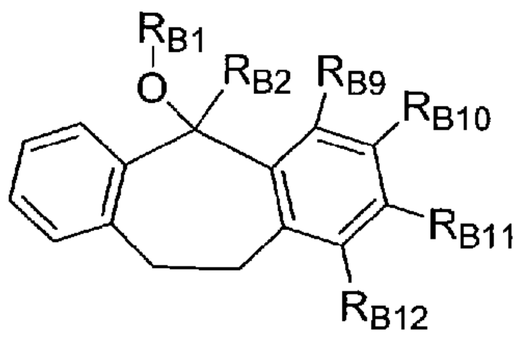
33. The compound of claim 31, wherein R_{B2} is C_{1-3} alkyl, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

34. The compound of claim 31, wherein R_{B2} is C_{1-3} alkenyl, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

35. The compound of claim 31, wherein R_{B2} is ethynyl, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

36. The compound of claim 31, wherein R_{B3} and R_{B4} are each H, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

37. The compound of claim 31, having the following structure

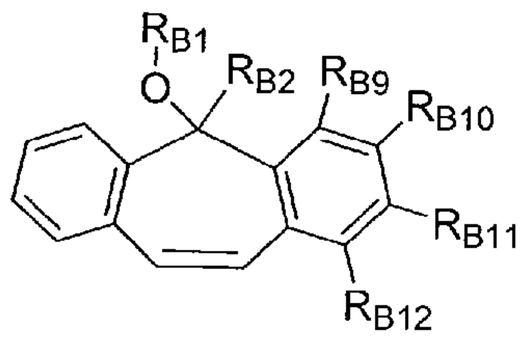


(III-A), wherein

R_{B2} is ethyl, ethenyl, or ethynyl and each R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H and halogen, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

38. The compound of claim 37, wherein R_{B10} or R_{B12} is fluoro, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

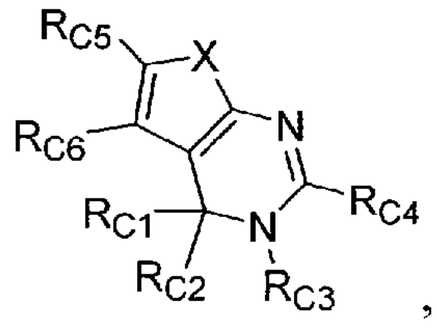
39. The compound of claim 31, having the following structure



(III-B), wherein

R_{B2} is ethyl, ethenyl, or ethynyl and each R_{B9}, R_{B10}, R_{B11}, and R_{B12} is selected, independently, from H and halogen, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

40. A compound having a structure according to the following formula



, wherein

each R_{C1}, R_{C2}, and R_{C3} is selected, independently, from H, optionally substituted C_{1-6} alkyl, -Y-R_{C7}, or R_{C1} and R_{C2} combine to form a (=O) or a (=S) group, or R_{C1} and R_{C3} combine to form a carbon-nitrogen double bond;

R_{C4} is selected from H, halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or -C(=O)ZR_{C8},

each R_{C5} and R_{C6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, or R_{C5} and R_{C6} combine to form an optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{C7}, R_{C8}, R_{C9}, R_{C10}, R_{C11}, and R_{C12} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

X is –CR_{C11}=CR_{C12}-, O, S, or NR_{C9};

Y is, independently, a single bond, $(CR_{C8}R_{C9})_n$, O, S, or NR_{C10}; and

Z is a single bond, O, S, or NR_{C10};

n is an integer between 0-4; and

wherein when X is S, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} combine to form unsubstituted cyclopentyl, R_{C3} is not -CH_2-R_{C7}, where R_{C7} is unsubstituted phenyl, unsubstituted naphthyl, unsubstituted 8-quinolyl, unsubstituted 2-oxoquinolyl, or phenyl having 1 or 2 substituents selected from F, OMe, Me, CN, or Cl;

wherein when X is S, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} are each CH_3, R_{C3} is not -CH_2-R_{C7}, where R_{C7} is unsubstituted phenyl; and

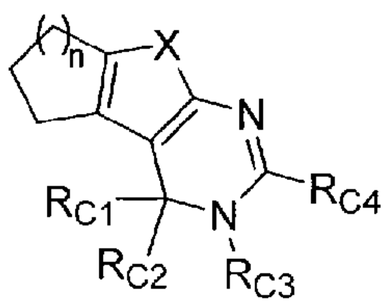
wherein when X is CH=CH, R_{C1} and R_{C2} combine to form a (=O) group, R_{C4} is H, and R_{C5} and R_{C6} are H, R_{C3} is not -CH_2(4-halophenyl);

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

41. The compound of claim 40, wherein each R_{C5} and R_{C6} is optionally substituted C_{1-6} alkyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

42. The compound of claim 40, wherein said compound has a structure according to the following formula



(IV-A), wherein X, R_{C1}, R_{C2}, R_{C3}, and R_{C4} are as defined for Formula (IV) and n is an integer between 0-3,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

43. The compound of claim 42, wherein R_{C1} and R_{C2} combine to form a (=O) group,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

44. The compound of claim 42, wherein X is S,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

45. The compound of claim 42, wherein n is 1,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

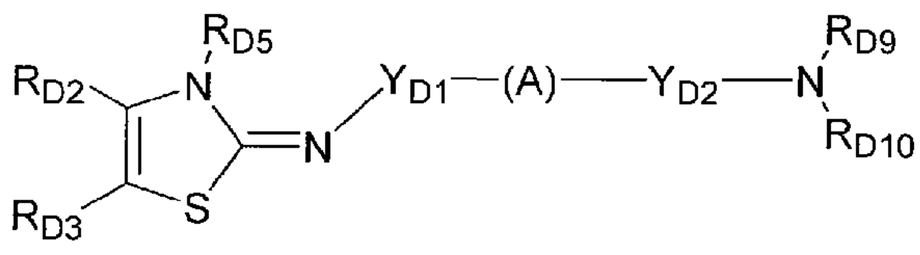
46. The compound of claim 45, wherein R_{C3} is -Y-R_{C7},

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

47. The compound of claim 46, wherein R_{C3} is –(CH_2)-(optionally substituted aryl),

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

48. A compound having a structure according to the following formula



(V-A), wherein

each Y_{D1} and Y_{D2} is selected, independently, from -C(=O)- or -$S(=O)_2$-;

A is phenyl having 0, 1, 2, 3, or 4 additional substituents;

R_{D2} and R_{D3} are selected, independently from H, halogen, CN, NC, N_3, NO_2, -COR_{D13}, -CO_2R_{D13}, -$CONR_{D13}R_{D14}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R_{D5}, R_{D9}, R_{D10}, R_{D13}, and R_{D14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{D9} and R_{D10} combine to form a heterocyclyl; and

wherein when R_{D2}, R_{D3}, and R_{D5} are H, Y_{D1} is –(C=O)-, Y_{D2} is –(SO_2)-, and R_{D9} and R_{D10} are each ethyl or R_{D9} is methyl and R_{D10} is CH_2(2-tetrahydrofuran), and A is phenyl having 0 additional substituents, Y_{D1} and Y_{D2} are not para to each other,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

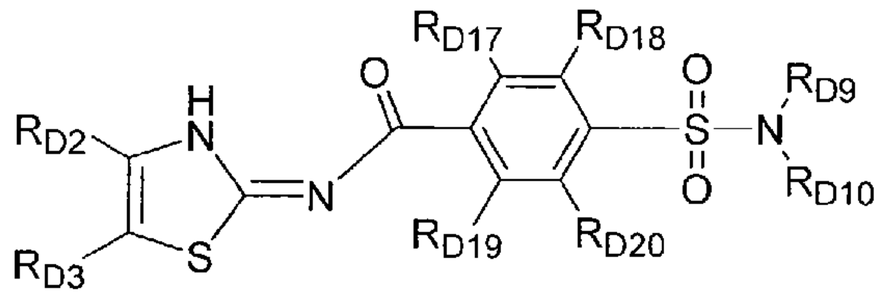
49. The compound of claim 48, wherein Y_{D1} and Y_{D2} are *ortho* or *meta* to each other,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

50. The compound of claim 48, wherein Y_{D1} and Y_{D2} are *para* to each other,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

51. The compound of claim 50, having a structure according to the following formula



(V-B), wherein

each R_{D2}, R_{D3}, R_{D17}, R_{D18}, R_{D19}, and R_{D20}, is selected, independently from H, halogen, CN, NC, N_3, NO_2, $-COR_{D13}$, $-CO_2R_{D13}$, $-CONR_{D13}R_{D14}$, optionally substituted C_{1-6} alkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R_{D9} and R_{D10} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, or optionally substituted aryl, or R_{D9} and R_{D10} combine to form a heterocyclyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

52. The compound of claim 51, wherein R_{D17}, R_{D18}, R_{D19}, and R_{D20} are H,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

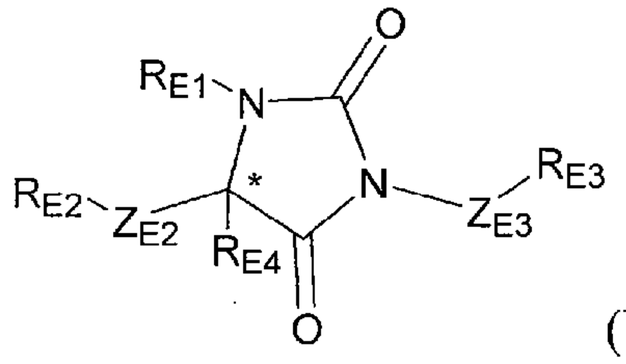
53. The compound of claim 51, wherein R_{D2} and R_{D3} are H,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

54. The compound of claim 53, wherein R_{D9} and R_{D10} are each optionally substituted C_{1-6} alkyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

55. A compound having a structure according to the following formula



(VI-A), wherein

each Z_{E2} and Z_{E3} is selected, independently, from a single bond, $-(CR_{E6}R_{E7})_n-$, -C(=O)-, or R_{E1} and Z_{E2}-R_{E2} combine to form a double bond;

each R_{E1}, R_{E2}, and R_{E4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R_{E3} is selected from optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

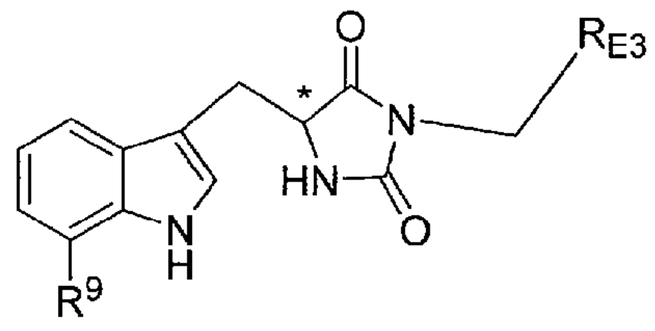
each R_{E6} and R_{E7} is selected, independently, from H or optionally substituted C_{1-6} alkyl; and

each n is an integer between 1-6; and

wherein when R_{E1} and R_{E4} are H, Z_{E2} and Z_{E3} are each CH_2, and R_{E2} is unsubstituted 3-indolyl, R_{E3} is not 4-chlorophenyl or $CH_2CH_2O(p\text{-}C_6H_4F)$,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

56. The compound of claim 55, wherein said compound has a structure according to the following formula:



(VI-D-3), wherein

R_{E3} is optionally substituted aryl or optionally substituted heteroaryl; and

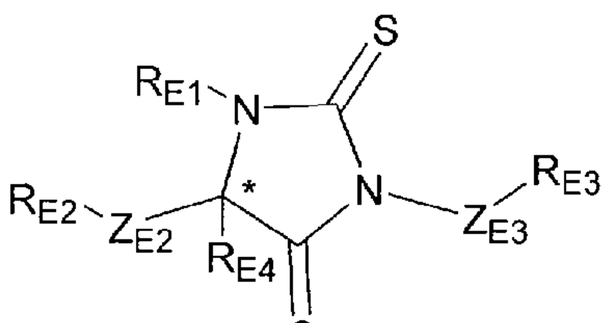
R^9 is H, halogen, CN, NO_2, OR^{13}, $NR^{13}R^{14}$, COR^{15}, CO_2R^{15}, or optionally substituted C_{1-6} alkyl;

each R^{13} and R^{14} is selected, independently, from H, COR^{16}, CO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and,

each R^{15} and R^{16} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

57. A compound having a structure according to the following formula



(VI-B), wherein

each Z_{E2} and Z_{E3} is selected, independently, from a single bond, $-(CR_{E6}R_{E7})_n-$, -C(=O)-, or R_{E1} and Z_{E2}-R_{E2} combine to form a double bond;

each R_{E1}, R_{E2}, and R_{E4} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally

substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R_{E3} is selected from optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

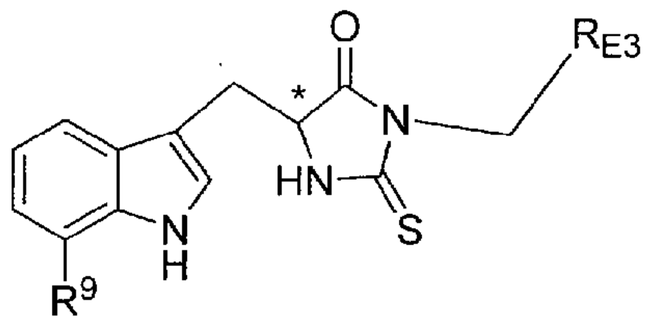
each R_{E6} and R_{E7} is selected, independently, from H or optionally substituted C_{1-6} alkyl; and

each n is an integer between 1-6; and

wherein when R_{E1} and R_{E4} are H, Z_{E2} is CH_2, and Z_{E3} is CH_2CH_2, R_{E2} is unsubstituted 3-indolyl, R_{E3} is not 4-morpholine,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

58. The compound of claim 57, wherein said compound has a structure according to the following formula:



(VI-D-4), wherein

R_{E3} is optionally substituted aryl or optionally substituted heteroaryl; and

R^9 is H, halogen, CN, NO_2, OR^{13}, $NR^{13}R^{14}$, COR^{15}, CO_2R^{15}, or optionally substituted C_{1-6} alkyl;

each R^{13} and R^{14} is selected, independently, from H, COR^{16}, CO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and,

each R^{15} and R^{16} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

59. The compound of any of claims 55-58, wherein R_{E3} is unsubstituted C_{3-10} cycloalkyl, unsubstituted heterocyclyl, unsubstituted aryl, or unsubstituted heteroaryl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

60. The compound of claim 59, wherein R_{E3} is unsubstituted aryl or heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

61. The compound of any of claims 55-58, wherein R_{E3} is substituted C_{3-10} cycloalkyl, substituted heterocyclyl, substituted aryl, or substituted heteroaryl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

62. The compound of claim 61, wherein said substituted C_{3-10} cycloalkyl, substituted heterocyclyl, substituted aryl, or substituted heteroaryl comprises 1, 2, 3, 4, or 5 substituents selected, independently, from the group consisting of: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, $-N_3$, -OR', -NR'C(=O)R", –C(=O)NRR', -NRR', -OC(=O)NR'R", -NRC(=O)OR', -OH, and -NC), wherein each R or R' is selected, independently, from II, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

63. The compound of claim 61, wherein R_{E3} is substituted aryl or substituted heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

64. The compound of claim 63, wherein R_{E3} is substituted phenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

65. The compound of claim 64, wherein said substituted phenyl is substituted with at least one halogen,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

66. The compound of claim 64, wherein said substituted phenyl is substituted with 1, 2, 3, 4, or 5 substituents selected, independently, from the group consisting of: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, $-N_3$, -OR', -NR'C(=O)R", –C(=O)NRR', -NRR', -OC(=O)NR'R", -NRC(=O)OR', -OH, and -NC), wherein each R or R' is selected, independently, from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

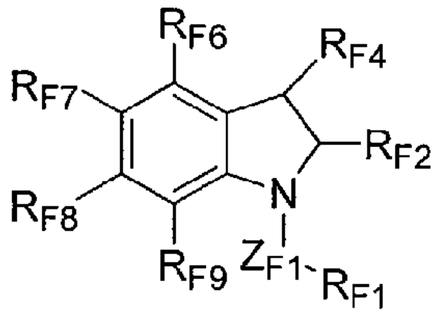
67. The compound of any of claims 55-58, wherein the stereocenter marked by the asterisk has the (*R*)-configuration,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

68. The compound of any of claims 55-58, wherein the stereocenter marked by the asterisk has the (*S*)-configuration,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

69. A compound having a structure according to the following formula,



(VII-A), wherein

Z_{F1} is selected from a single bond, -(CH_2)-, -C(=O)-, or -S(=O)$_2$-;

R_{F1} is selected from H, OR_{F14}, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R_{F2} and R_{F4} are each H, or R_{F2} and R_{F4} combine to form a carbon-carbon double bond;

each R_{F6}, R_{F7}, R_{F8}, and R_{F9} is selected, independently, from H, halogen, CN, NC, N_3, NO_2, OR_{F12}, SR_{F12}, $NR_{F12}R_{F13}$, -COR_{F12}, -CO_2R_{F12}, -$CONR_{F12}R_{F13}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each R_{F12}, R_{F13}, and R_{F14} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

wherein when R_{F2}, R_{F4}, R_{F6}, R_{F7}, R_{F8}, and R_{F9} are each H and Z_{F1} is -C(=O)-, R_{F1} is not -(unsubstituted 1,4-benzodioxane), -CH_2-O-(unsubstituted phenyl), or -CH(CH_3)O(*o*-tolyl);

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

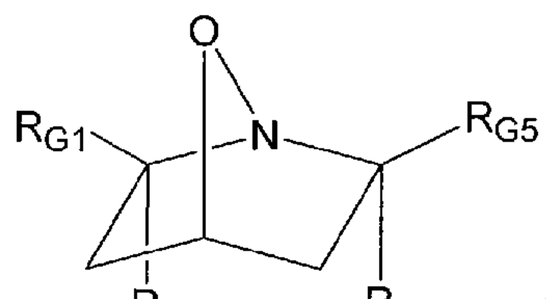
70. The compound of claim 69, wherein R_{F2} and R_{F4} are each H, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

71. The compound of claim 69, wherein R_{F6}, R_{F7}, R_{F8}, and R_{F9} are H, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

72. The compound of claim 69, wherein Z_{F1} is -C(=O)-, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

73. The compound of claim 72, wherein R_{F1} is optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

74. A compound having a structure according to the following formula



(VIII-A), wherein

each R_{G1}, R_{G2}, R_{G5}, and R_{G6} is selected, independently, from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or R_{G1} and R_{G2}, or R_{G5} and R_{G6} combine to form an optionally substituted cycloalkyl or heterocyclyl; and

wherein when R_{G1} is unsubstituted phenyl and R_{G2} is H, R_{G5} and R_{G6} do not combine to form unsubstituted cyclopentyl;

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

75. The compound of claim 74, wherein R_{G1} or R_{G5} is phenyl having 0, 1, 2, 3, 4, or 5 substituents,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

76. The compound of claim 75, wherein R_{G1} is unsubstituted phenyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

77. The compound of claim 74, wherein R_{G2} or R_{G6} is phenyl having 0, 1, 2, 3, 4, or 5 substituents,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

78. The compound of claim 74, wherein R_{G1} and R_{G2}, or R_{G5} and R_{G6} combine to form an optionally substituted cycloalkyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

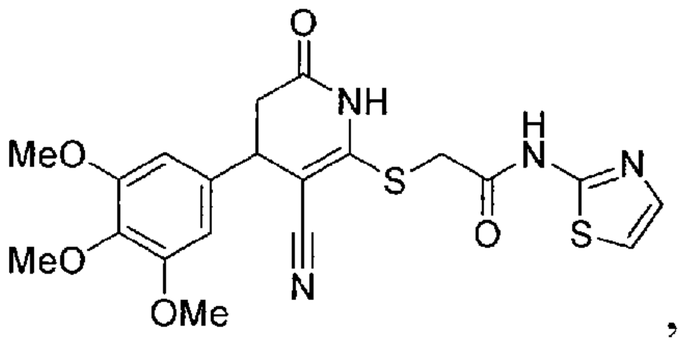
79. The compound of claim 78, wherein said cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl,

or any pharmaceutically acceptable salt or solvate thereof, or any stereoisomer thereof.

80. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound of any of claims 1-79, or any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70),

or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

81. The composition of claim 80, wherein said compound is selected from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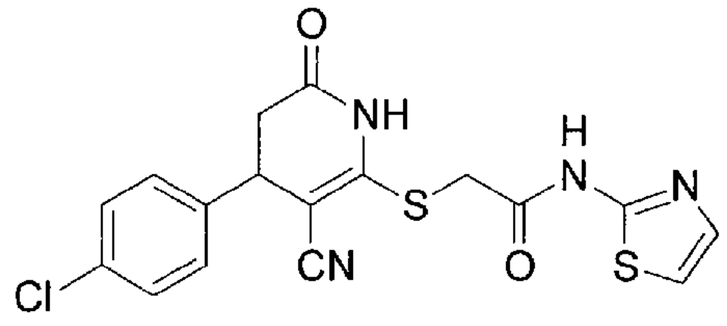
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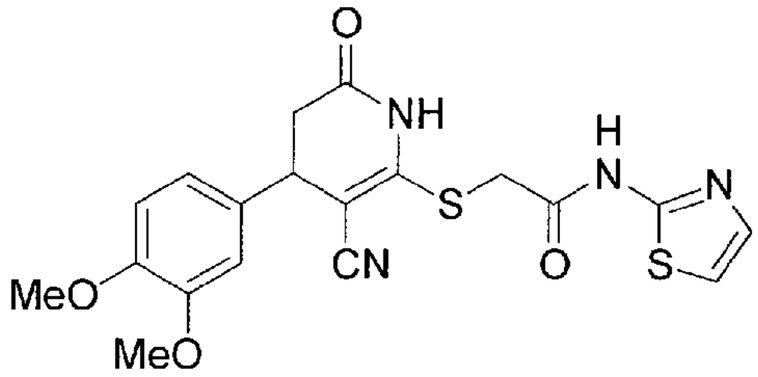
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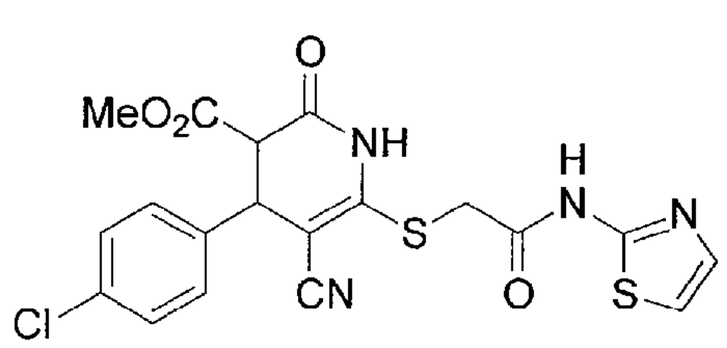
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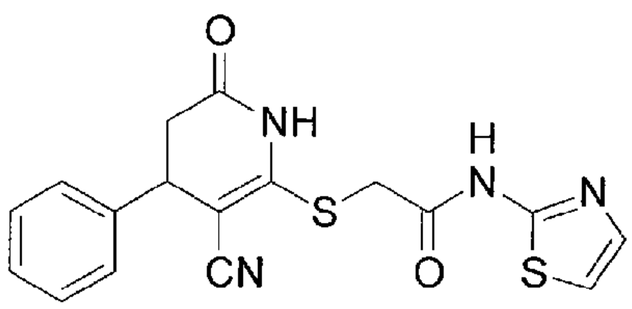
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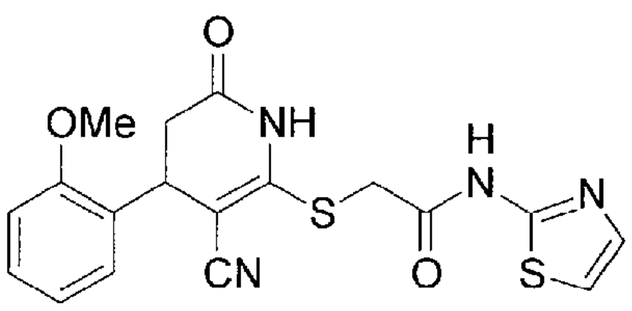
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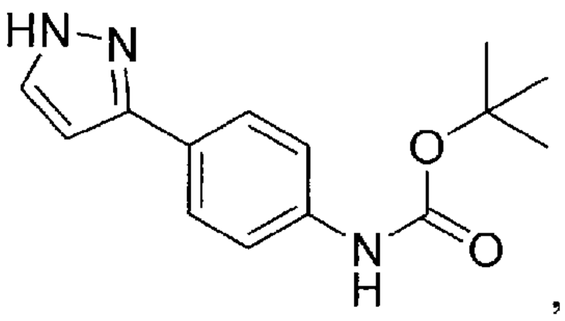
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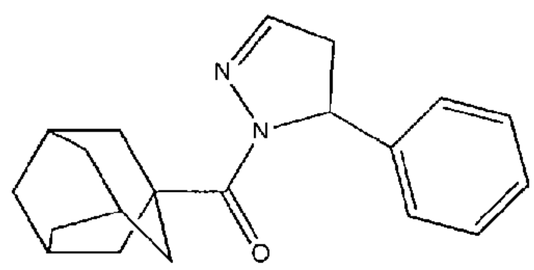
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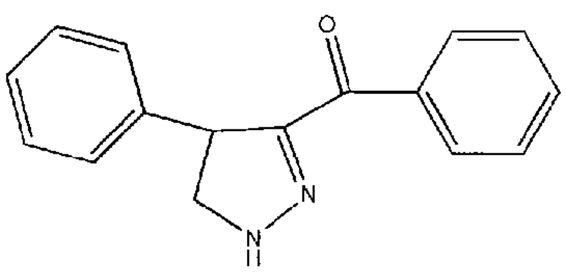
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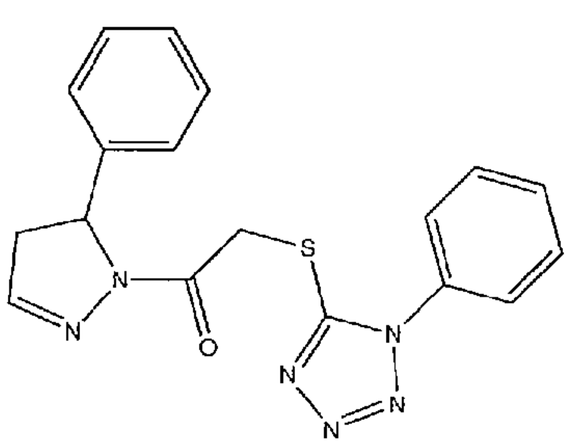
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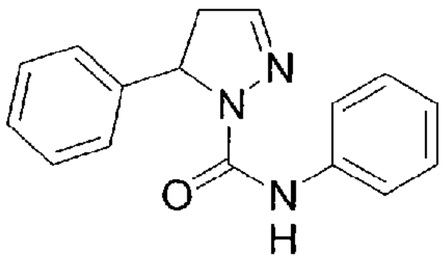
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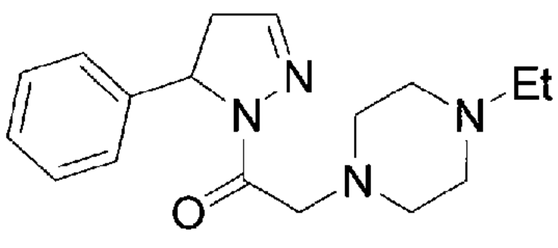
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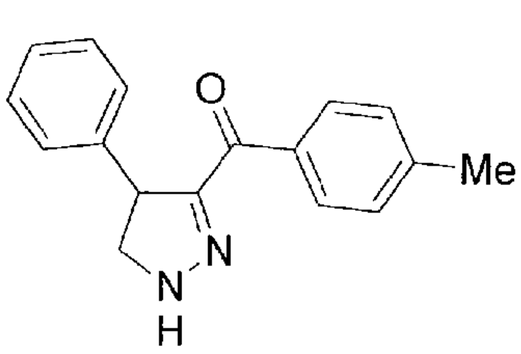
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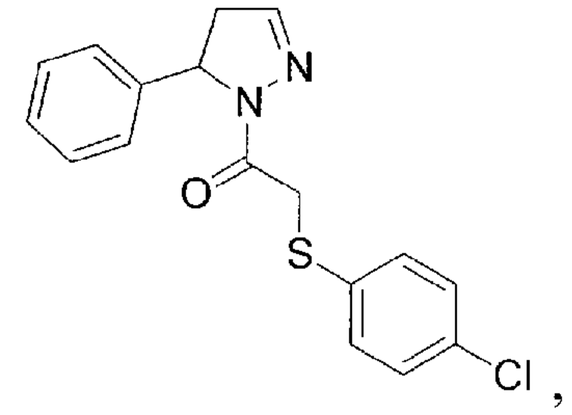
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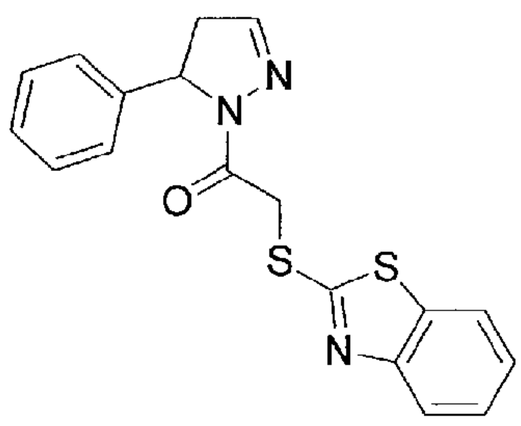
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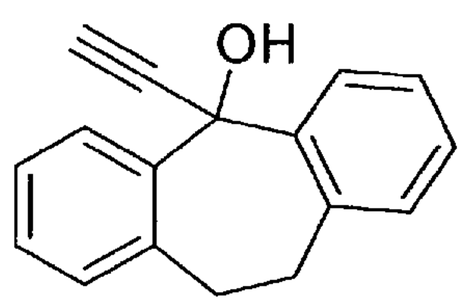
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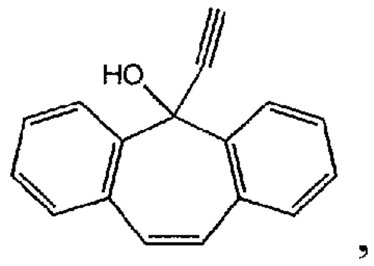
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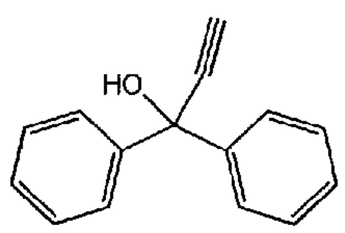
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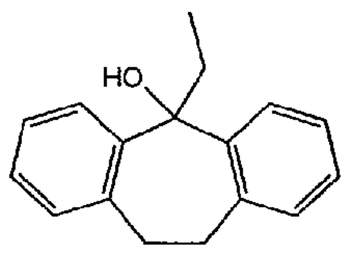
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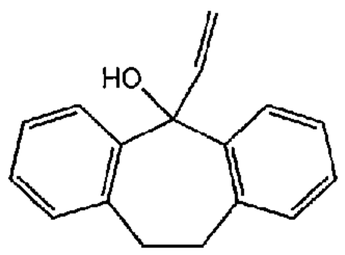
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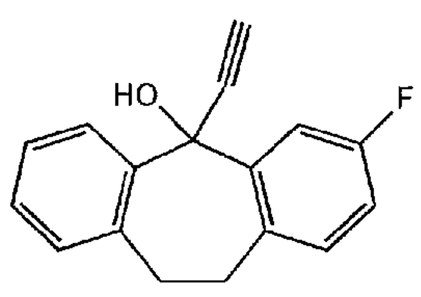
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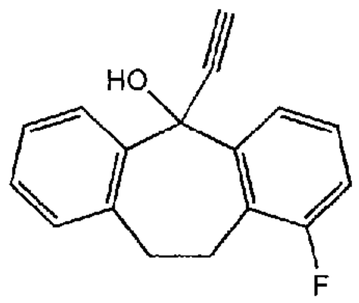
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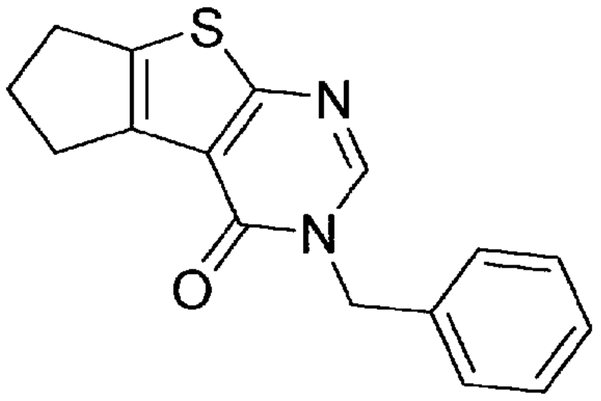
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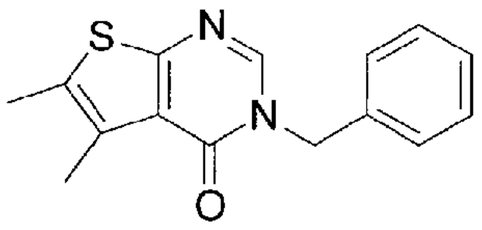
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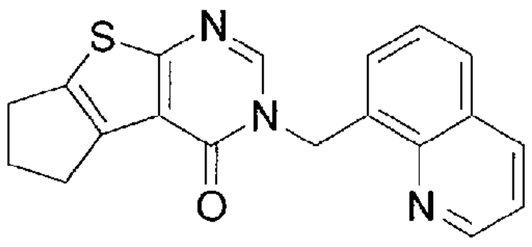
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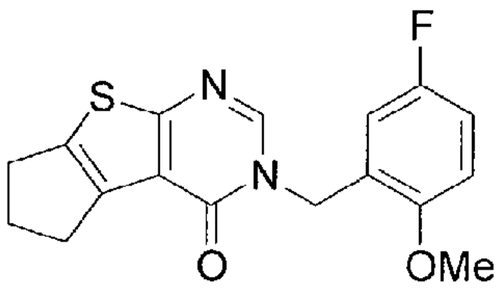
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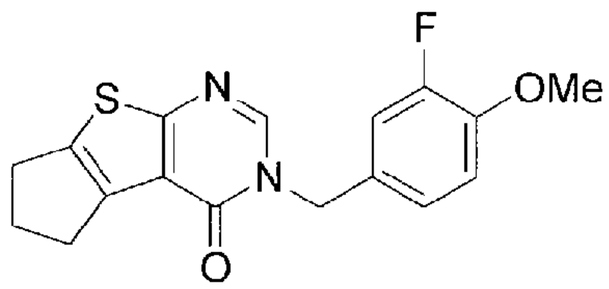
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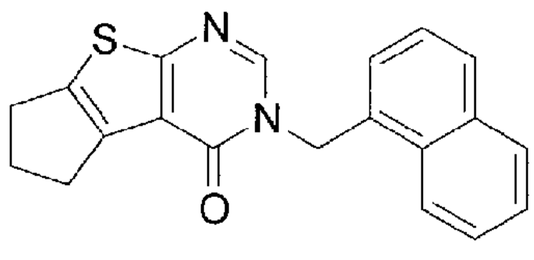
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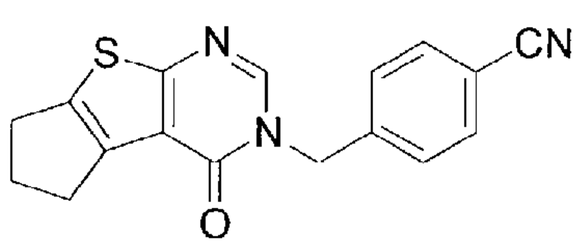
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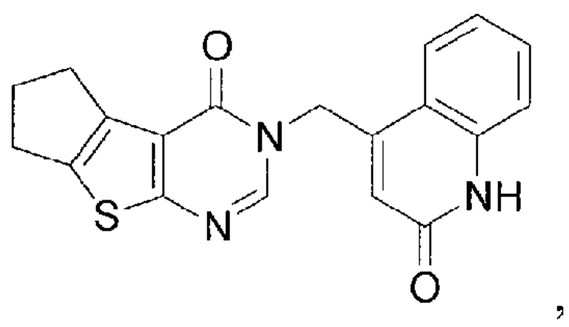
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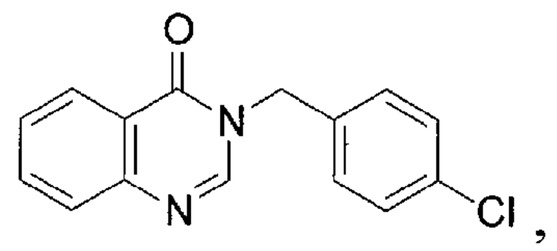
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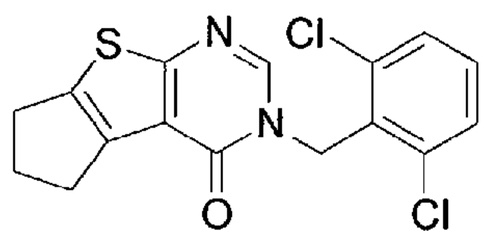
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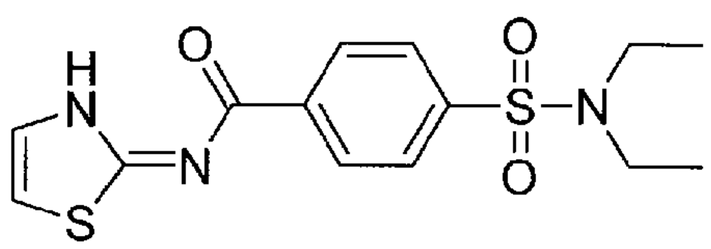
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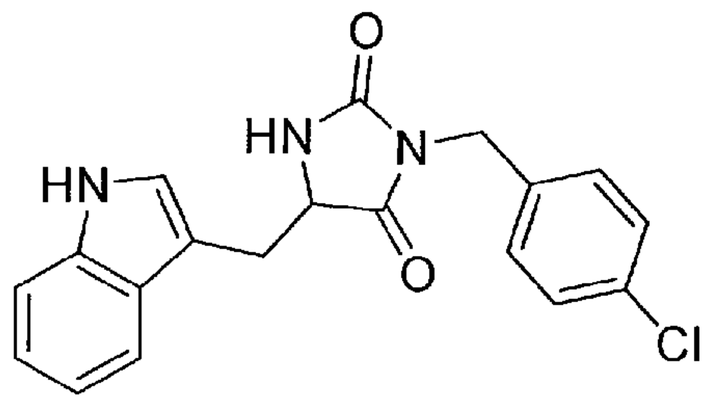
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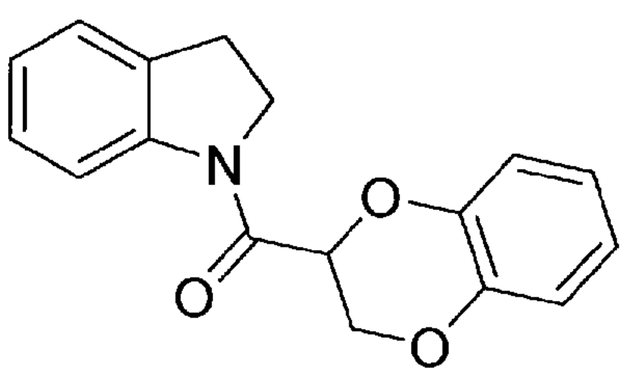
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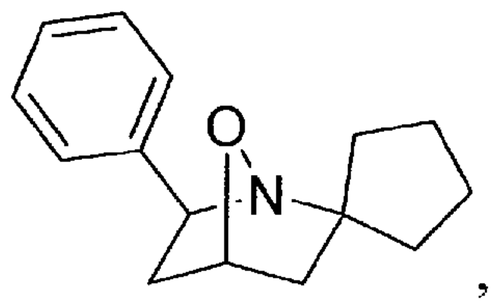
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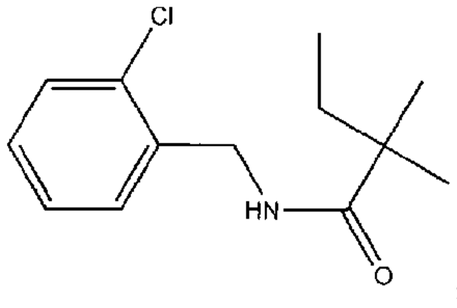
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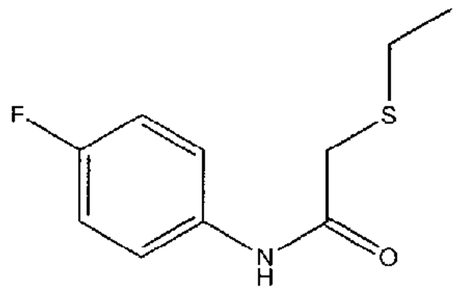
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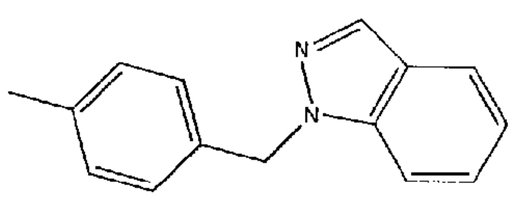
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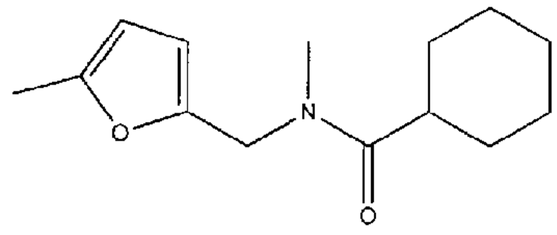
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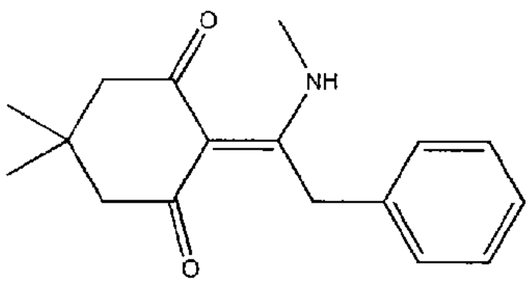
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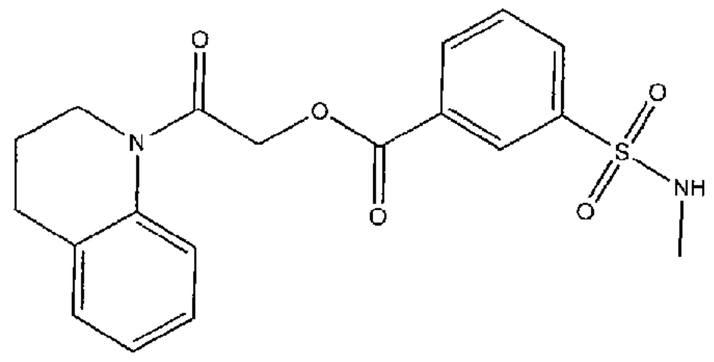
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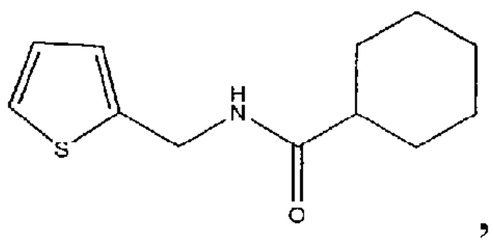
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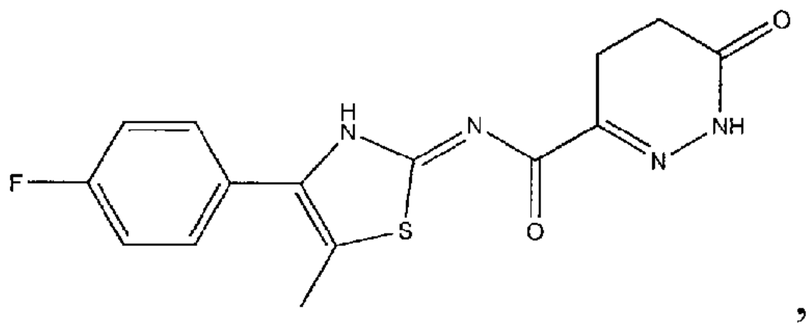
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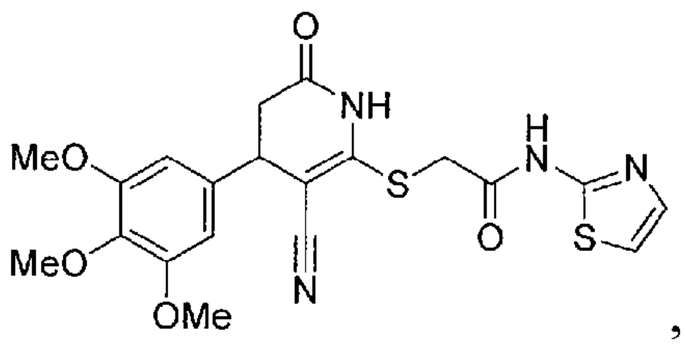
or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

82. A method of treating a condition in a subject, said method comprising the step of administering the compound of any of claims 1-79, or any compound of

Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70),

or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof, to said subject in a dosage sufficient to decrease necroptosis.

83. The method of claim 82, wherein said compound is selected from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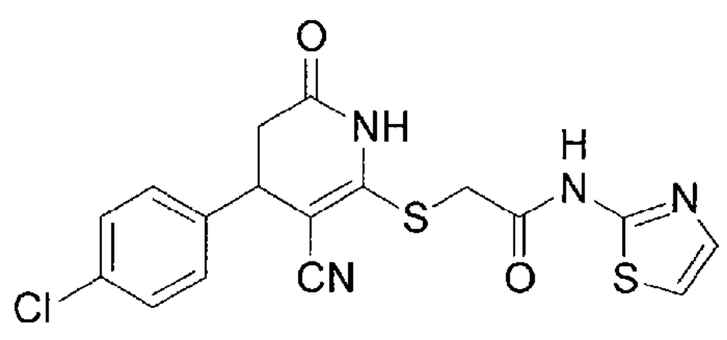
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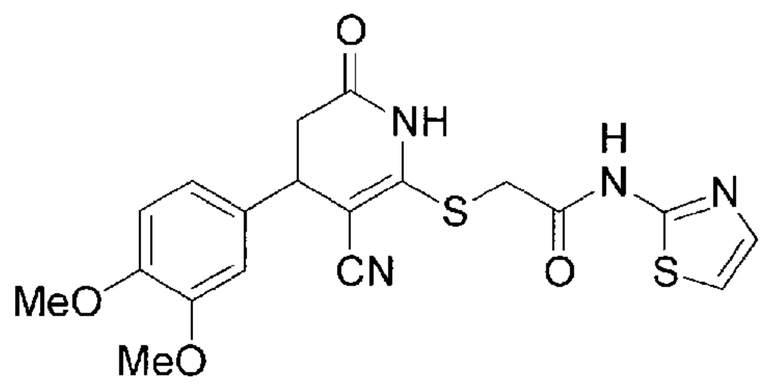
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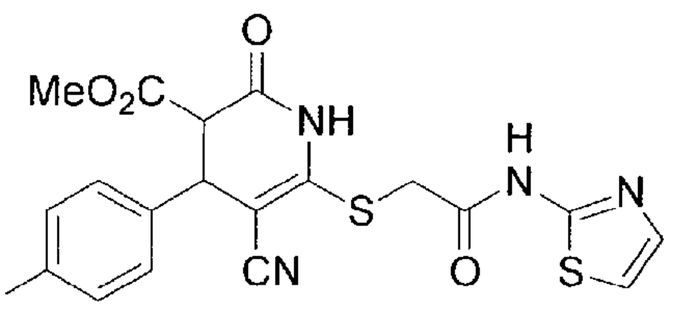
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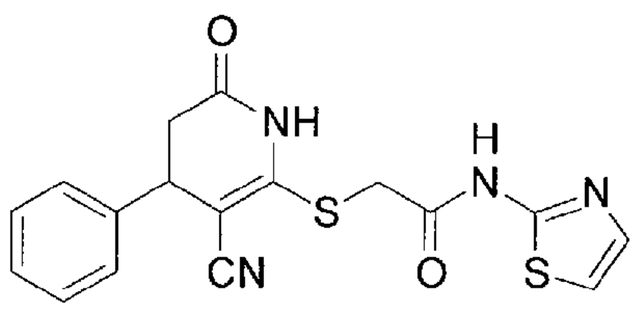
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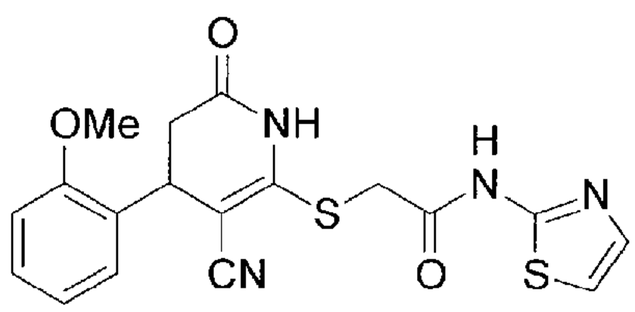
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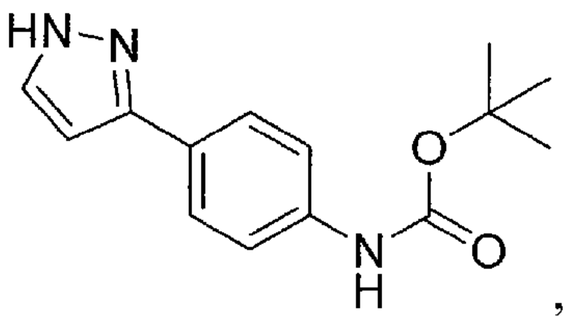
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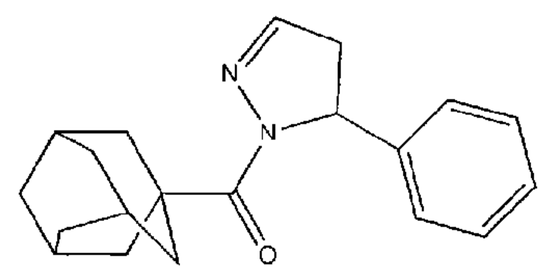
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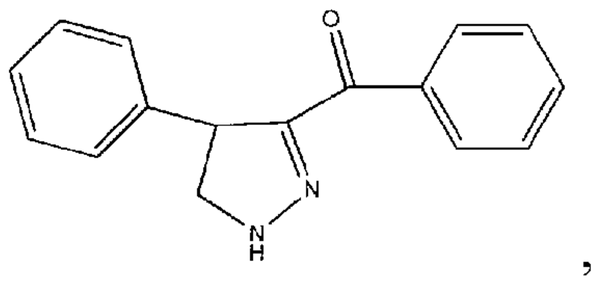
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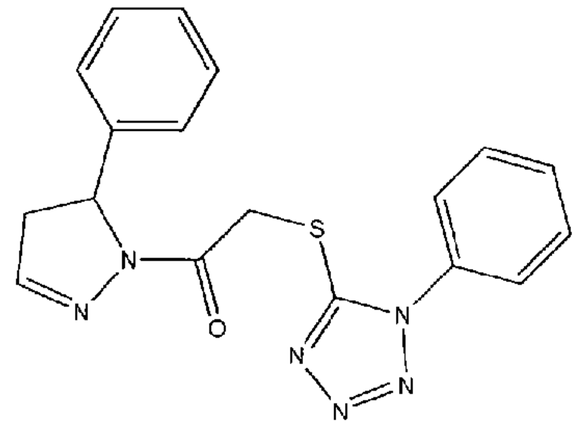
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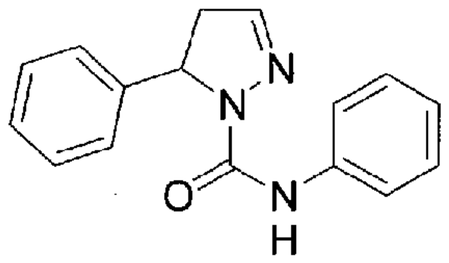
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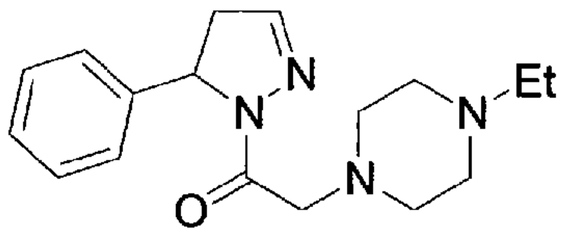
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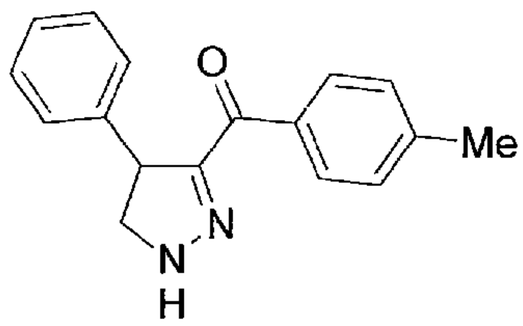
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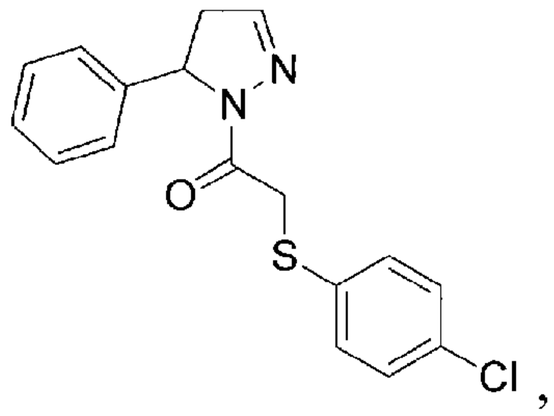
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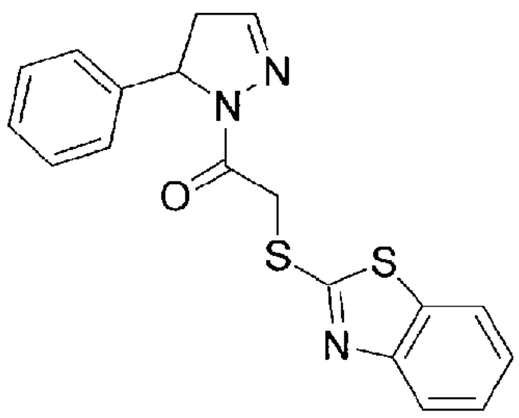
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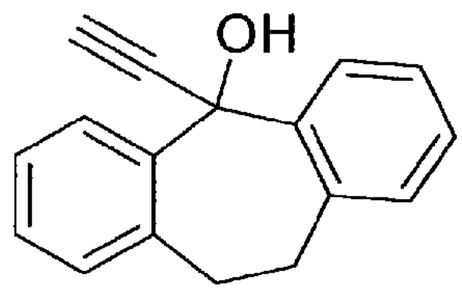
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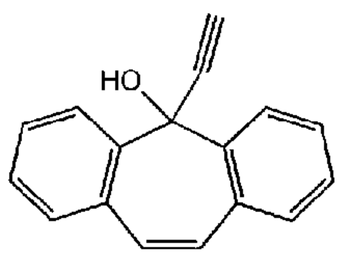
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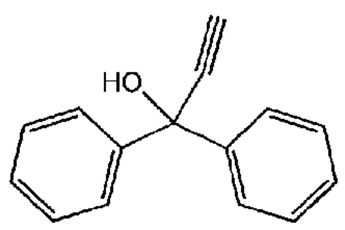
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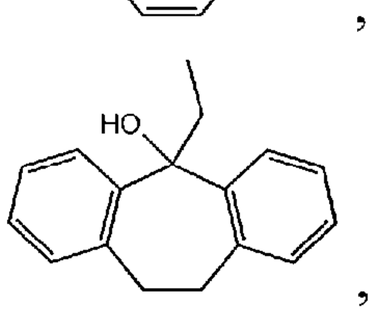
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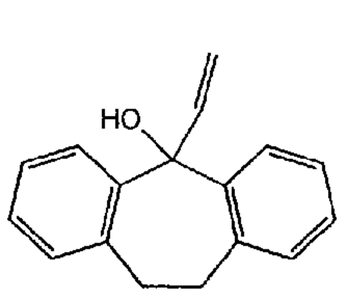
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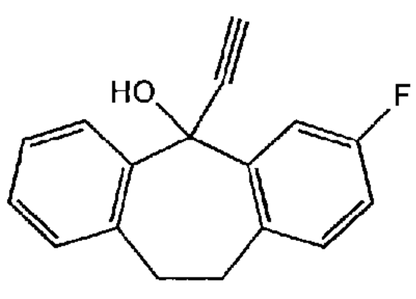
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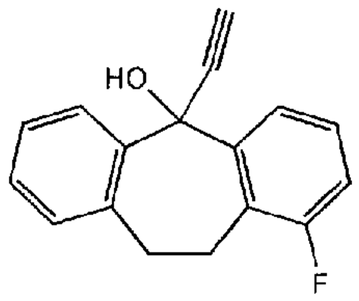
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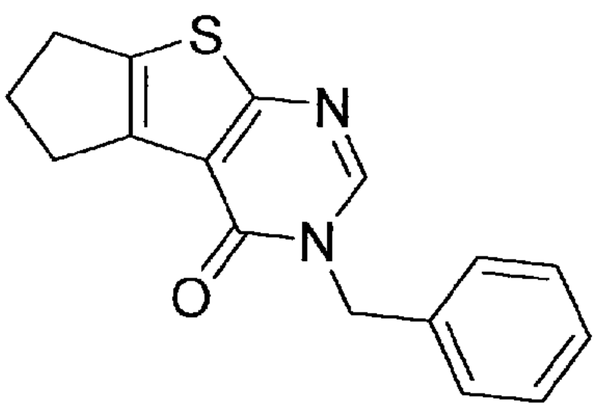
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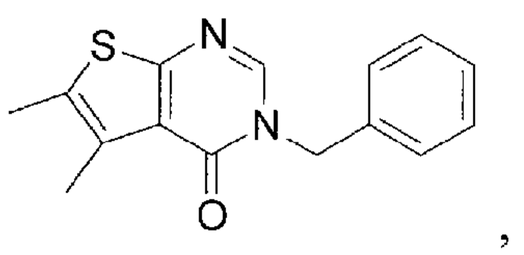
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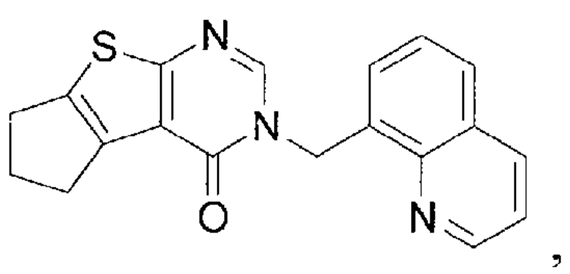
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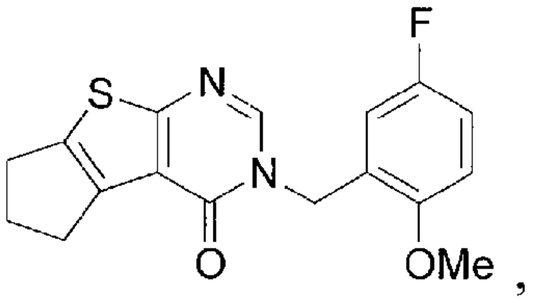
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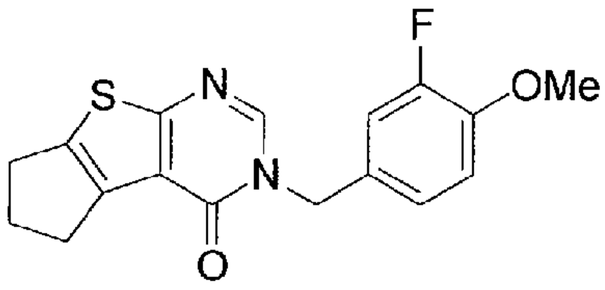
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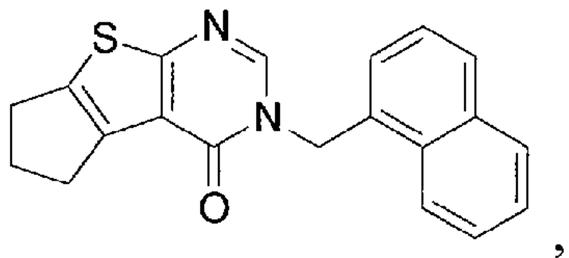
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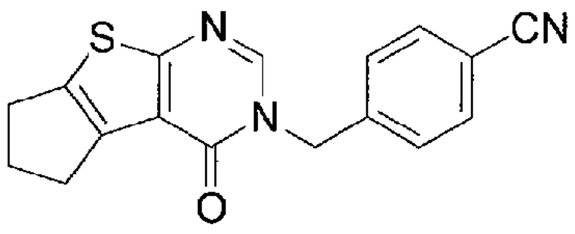
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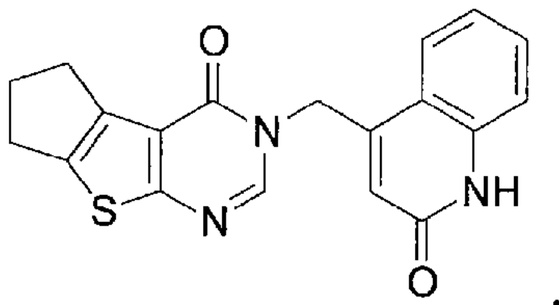
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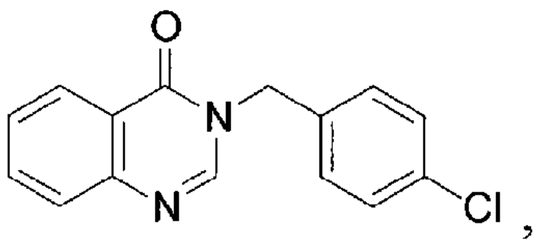
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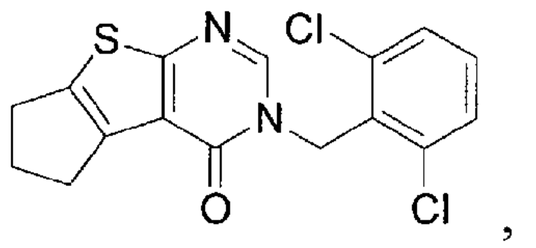
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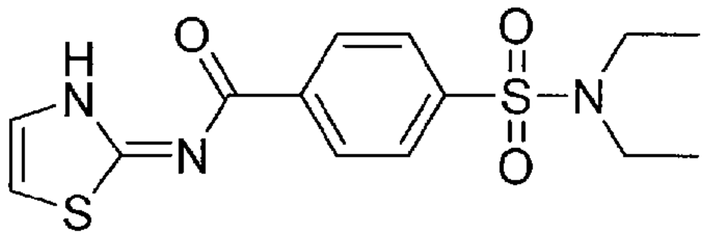
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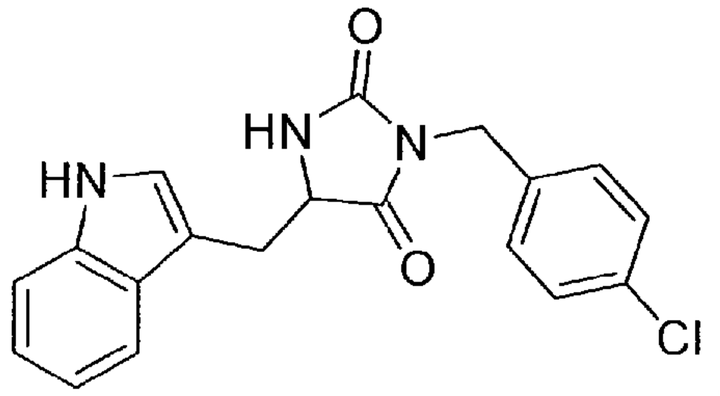
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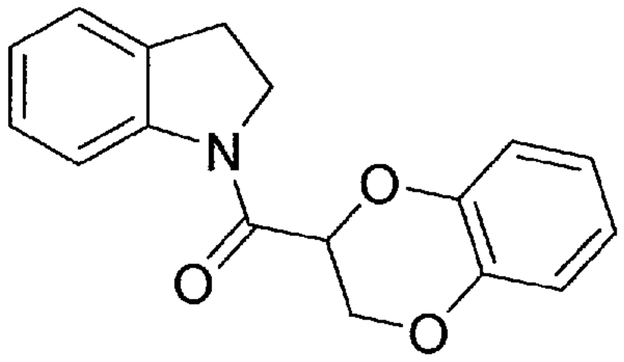
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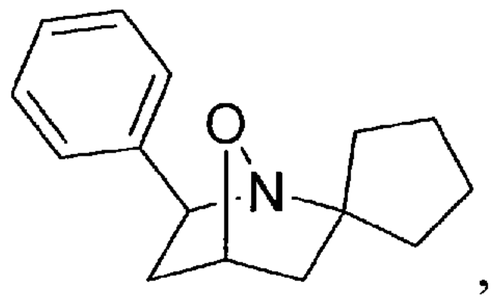
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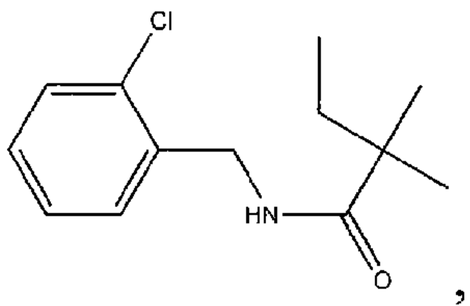
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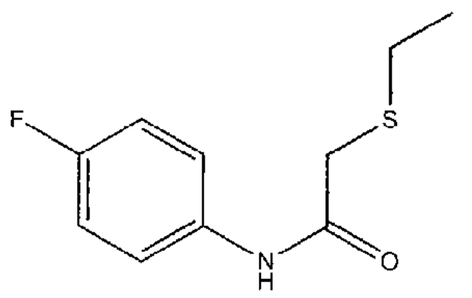
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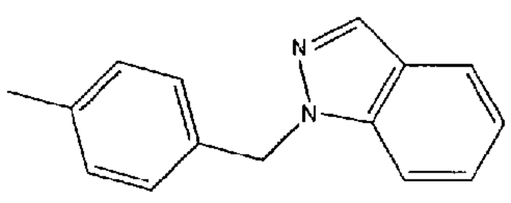
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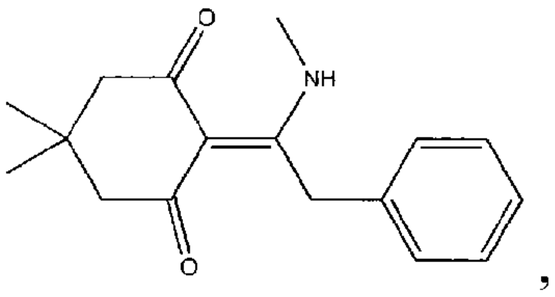
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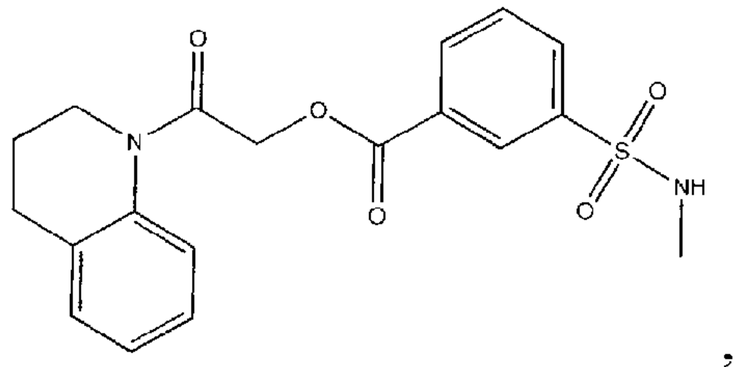
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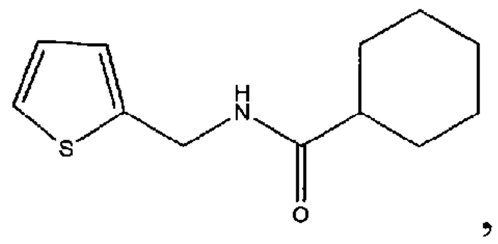
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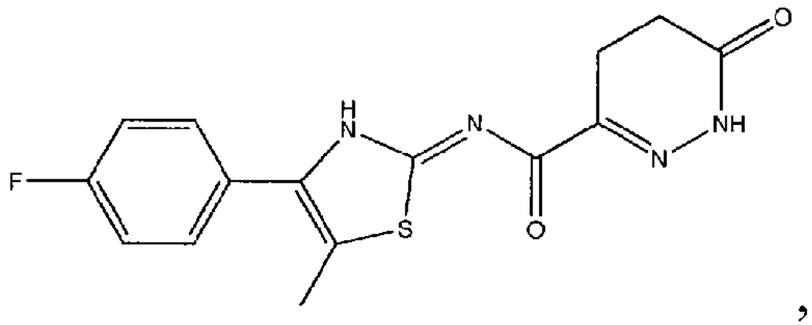
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or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

84. The method of claim 83, wherein said condition is a neurodegenerative disease of the central or peripheral nervous system, the result of retinal neuronal cell death, the result of cell death of cardiac muscle, the result of cell death of cells of the immune system; stroke, liver disease, pancreatic disease, the result of cell death associated with renal failure; heart, mesenteric, retinal, hepatic or brain ischemic injury, ischemic injury during organ storage, head trauma, septic shock, coronary heart disease, cardiomyopathy, myocardial infarction, bone avascular necrosis, sickle cell disease, muscle wasting, gastrointestinal disease, tuberculosis, diabetes, alteration of blood vessels, muscular dystrophy, graft-versus-host disease, viral infection, Crohn's disease, ulcerative colitis, asthma, or any condition in which alteration in cell proliferation, differentiation or intracellular signaling is a causative factor.

85. The method of claim 84, wherein said condition is a neurodegenerative disease of the central or peripheral nervous system.

86. The method of claim 84, wherein said condition is hepatic or brain ischemic injury, or ischemic injury during organ storage, head trauma, septic shock, or coronary heart disease.

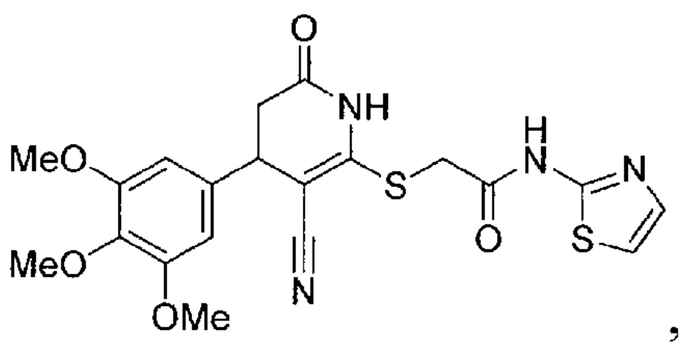
87. The method of claim 84, wherein said condition is stroke.

88. The method of claim 84, wherein said condition is myocardial infarction.

89. A method of decreasing necroptosis comprising contacting a cell with the compound of any of claims 1-79, or any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70)),

or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

90. The method of claim 89, wherein said compound is selected from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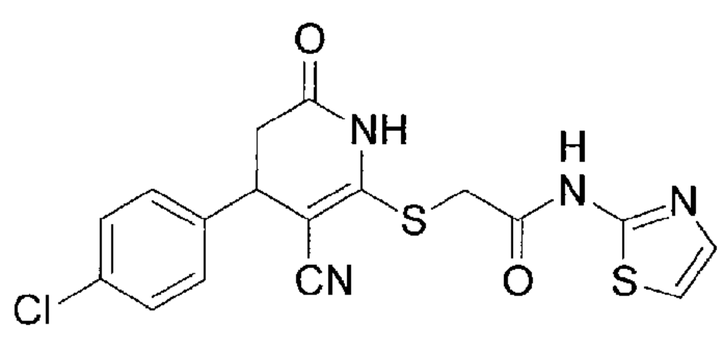
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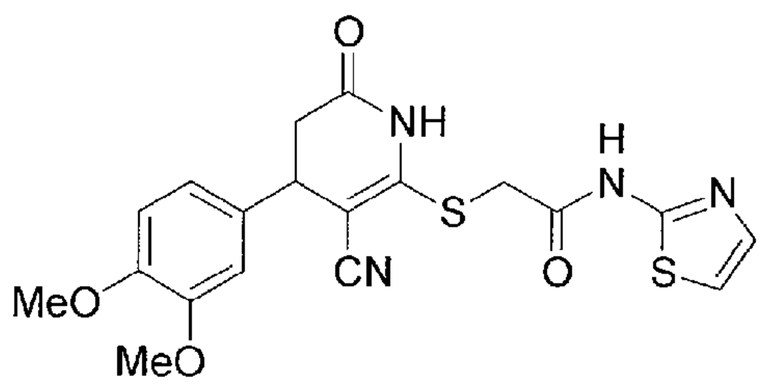
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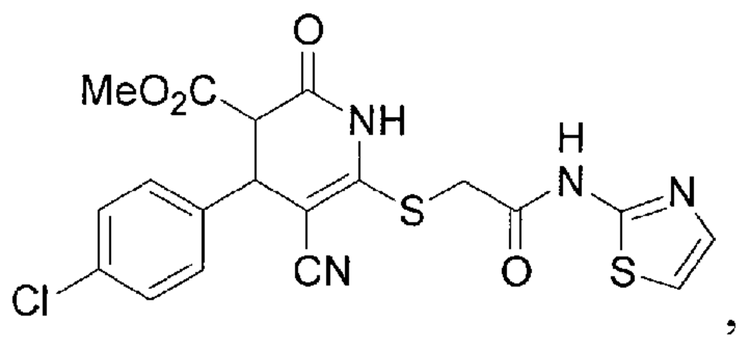
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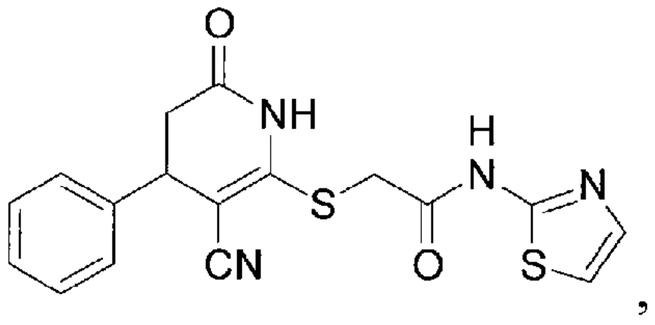
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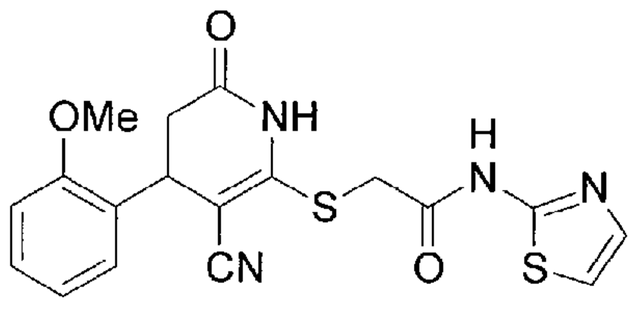
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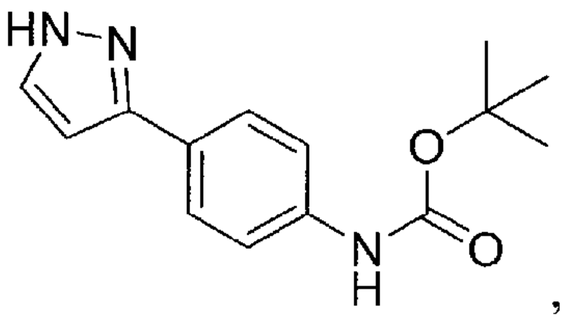
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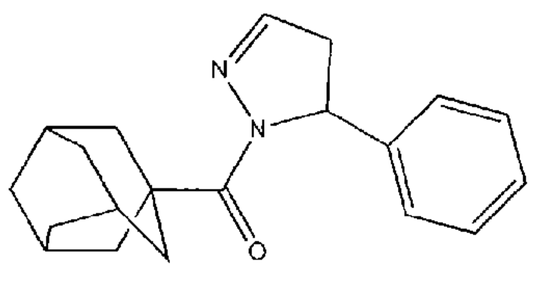
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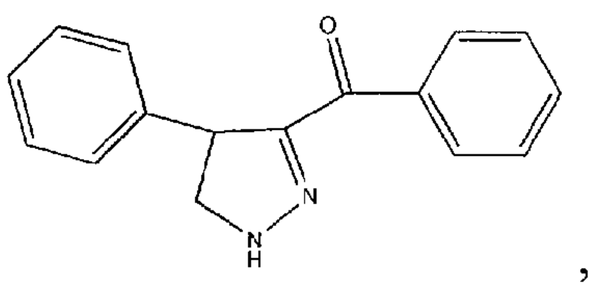
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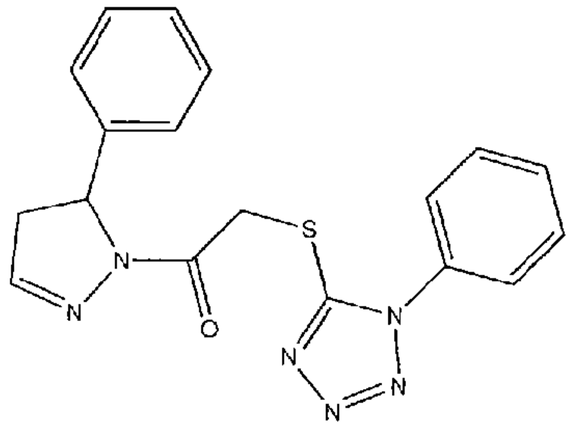
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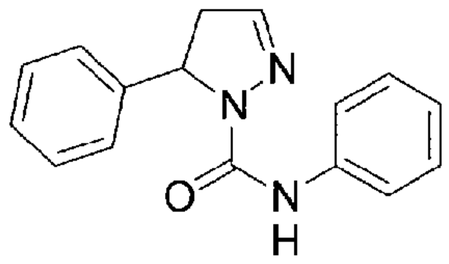
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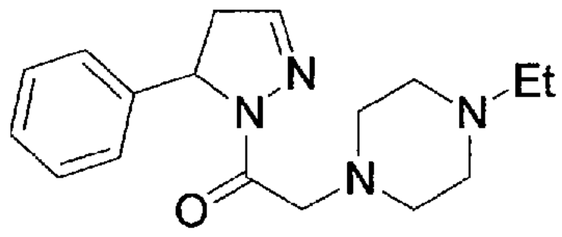
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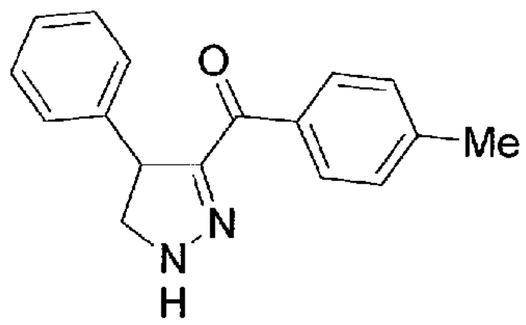
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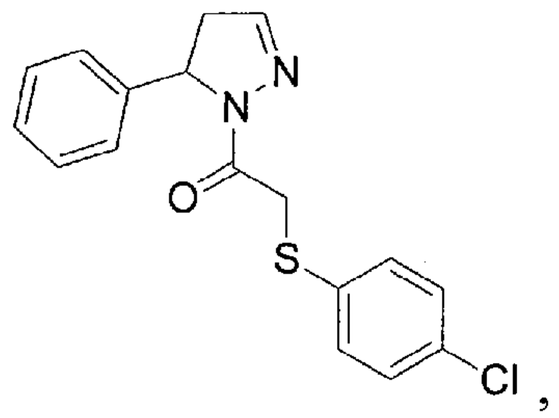
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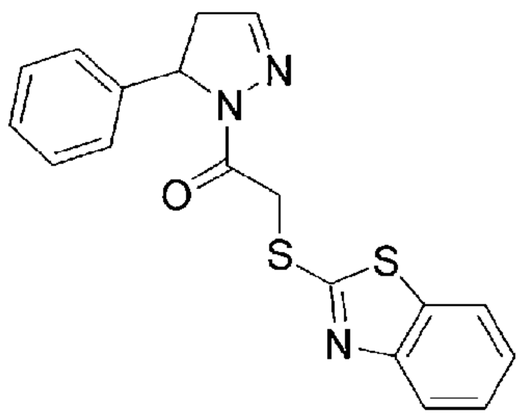
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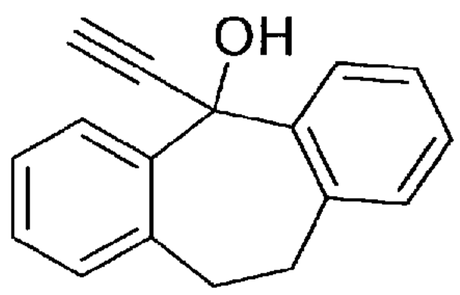
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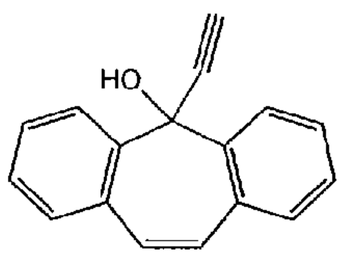
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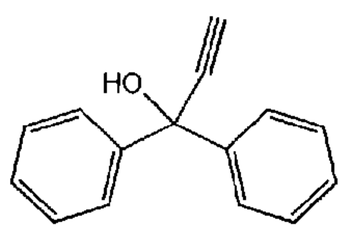
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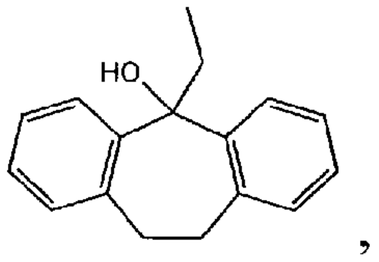
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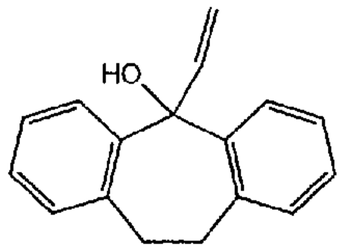
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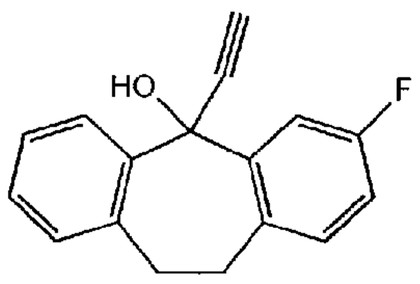
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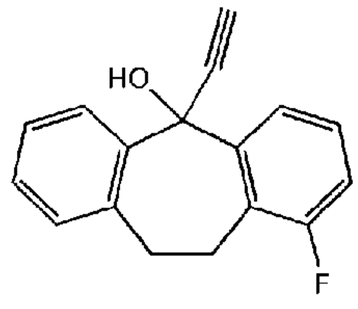
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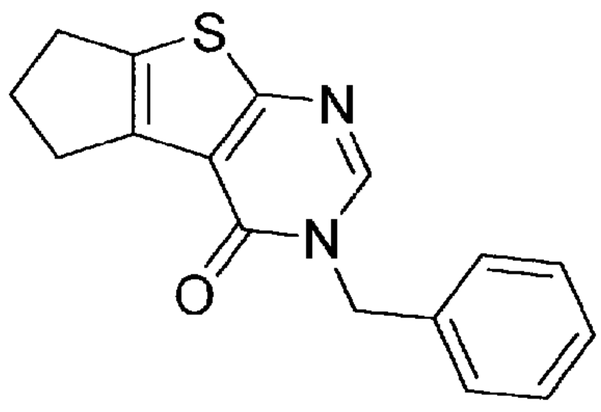
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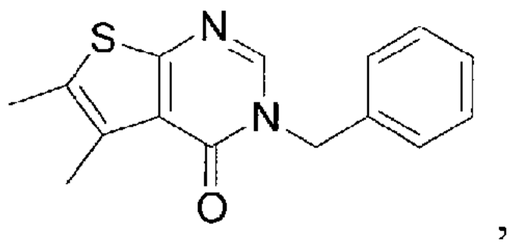
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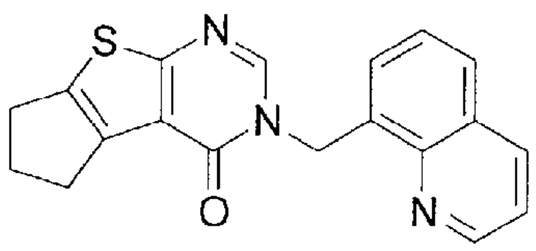
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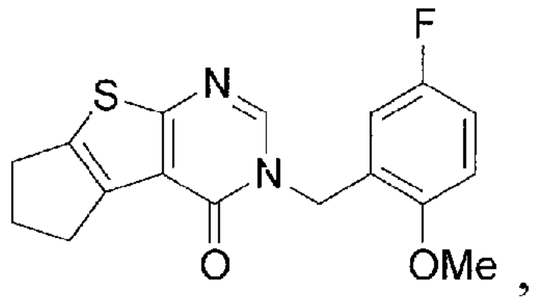
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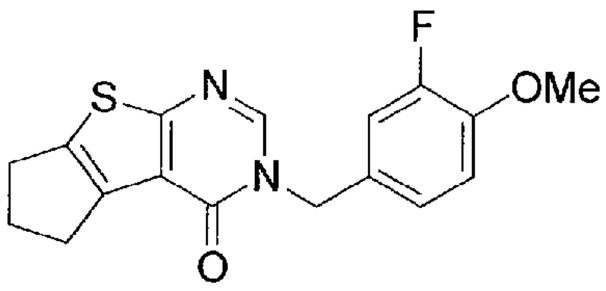
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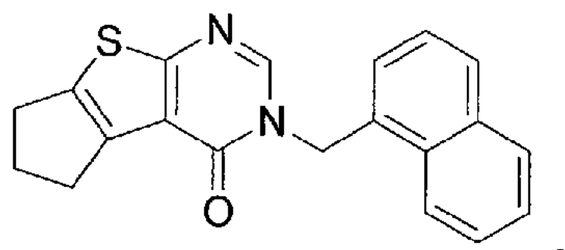
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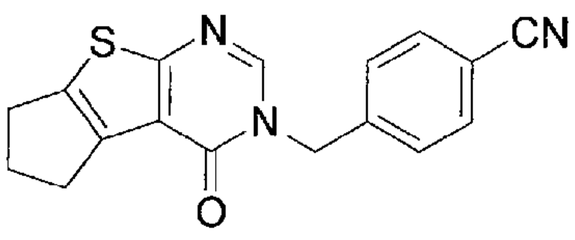
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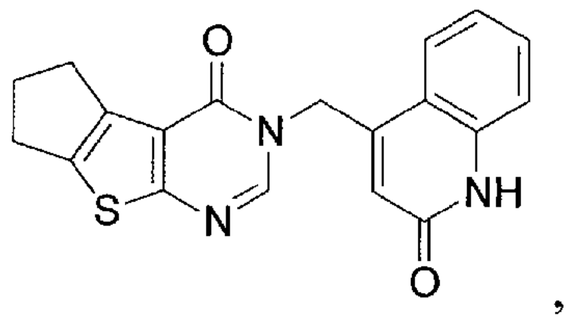
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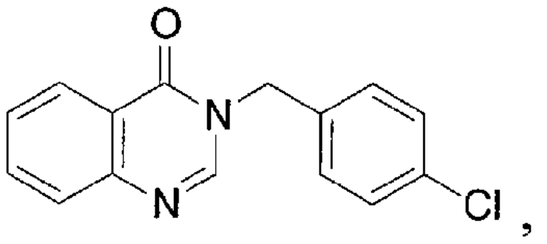
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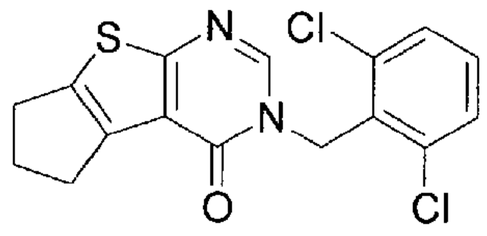
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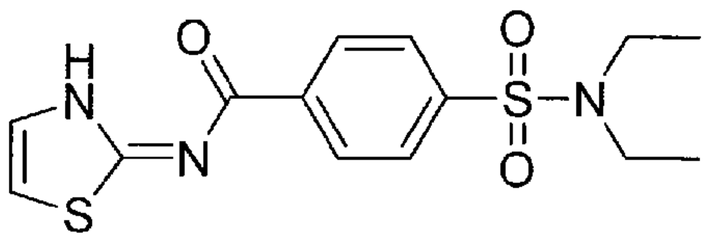
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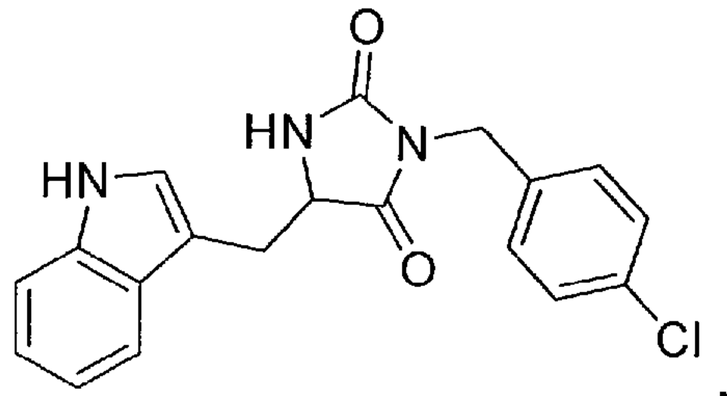
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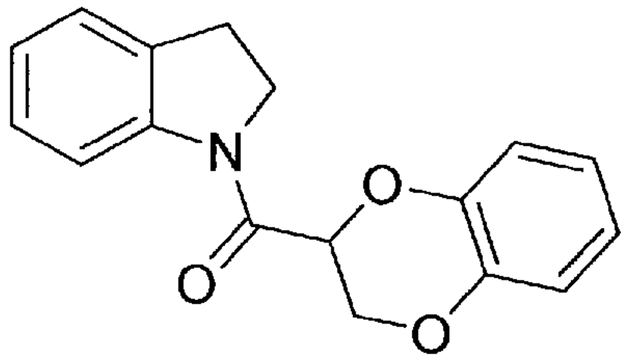
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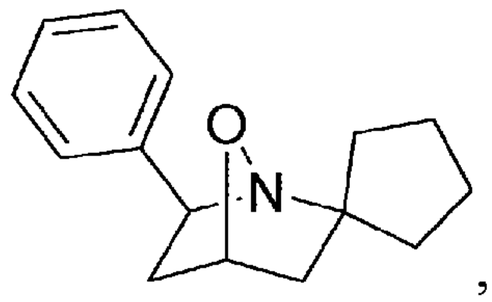
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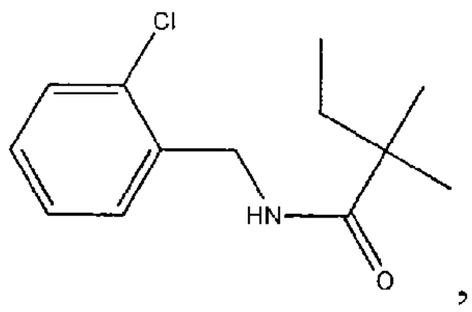
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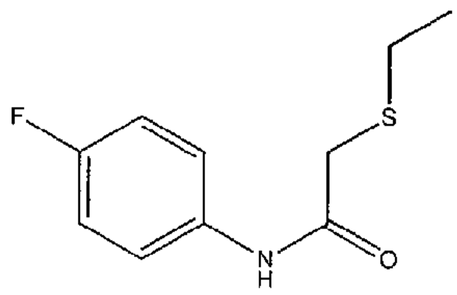
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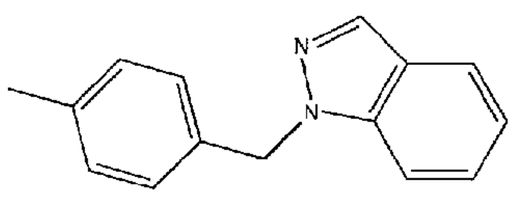
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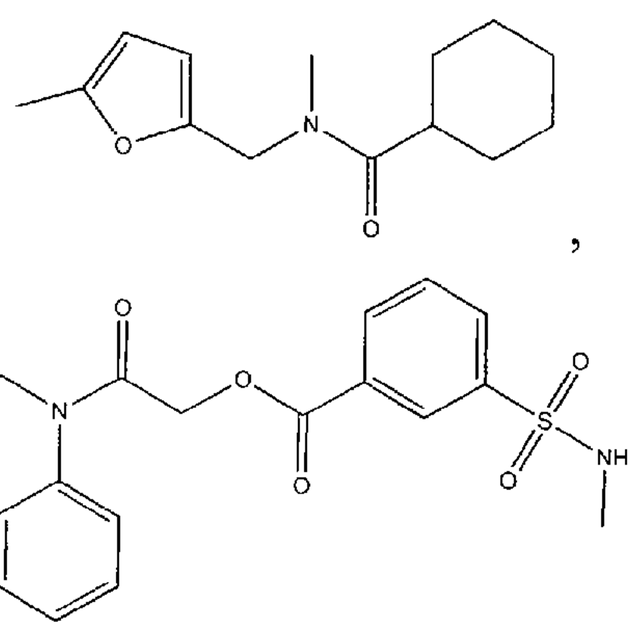
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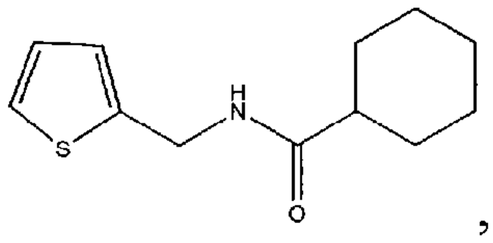
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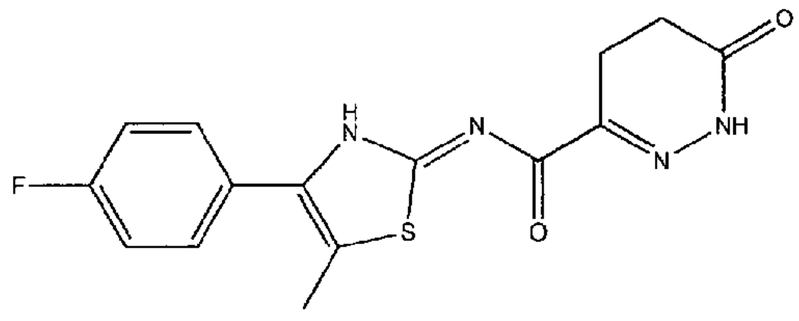
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or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof.

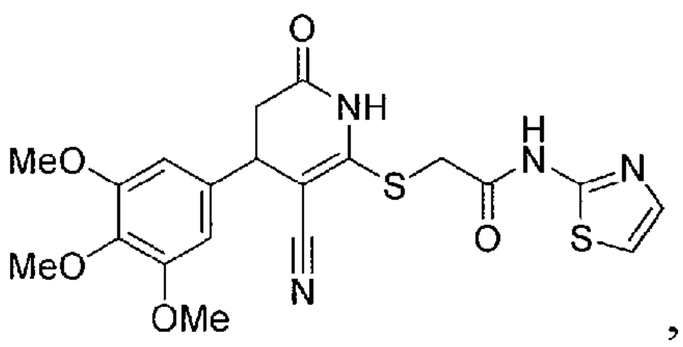
91. A kit comprising

(a) a pharmaceutically acceptable composition comprising the compound of any of claims 1-79, or any compound of Formulas (I)-(VIII), or any of Compounds (1)-(7), (13)-(26), (27)-(33), (48)-(57), and (58)-(70),

or any pharmaceutically acceptable salt or solvate thereof, or stereoisomer thereof; and

(b) instructions for the use of the pharmaceutical composition of (a) to treat a condition in a subject.

92. The kit of claim 91, wherein said compound of (a) is selected from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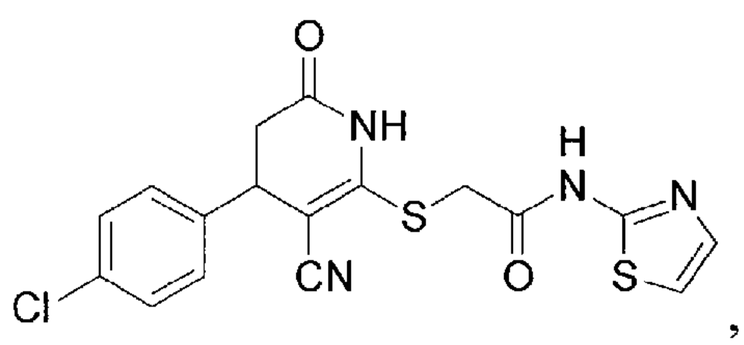
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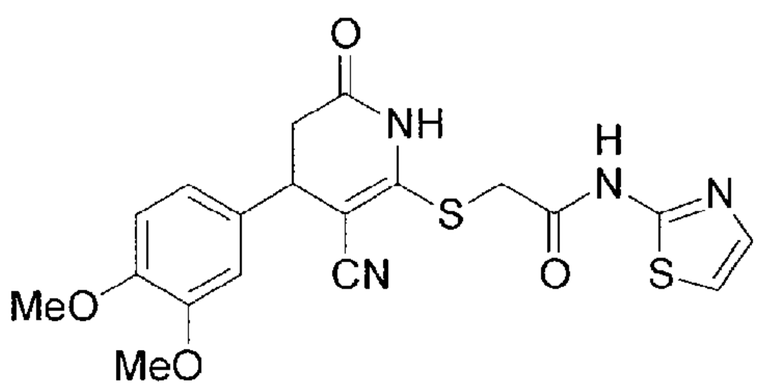
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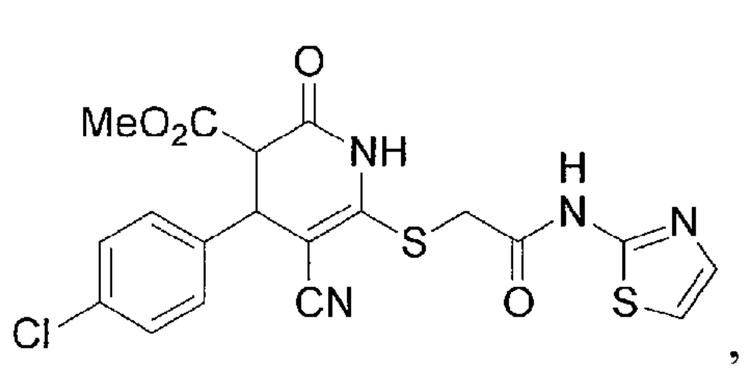
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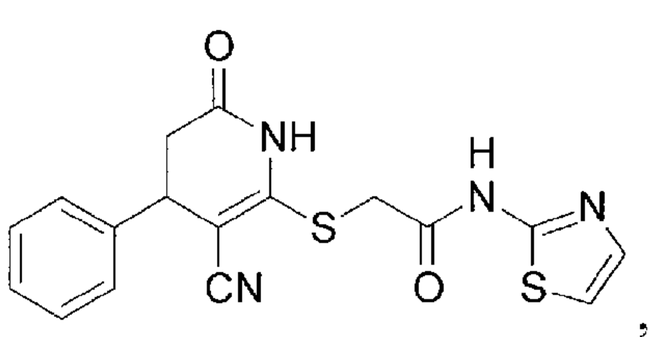
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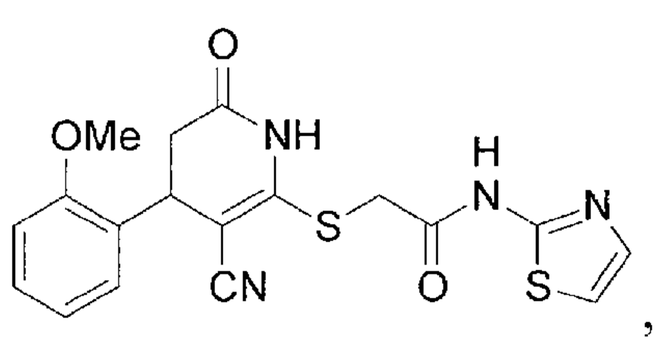
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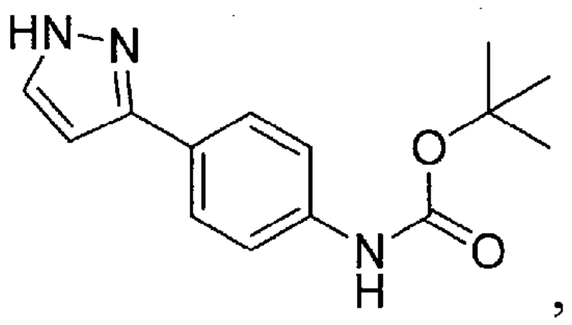
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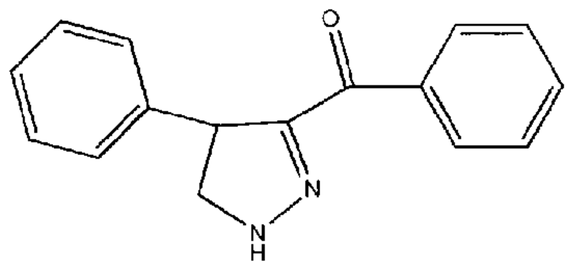
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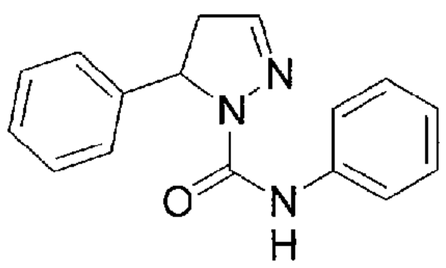
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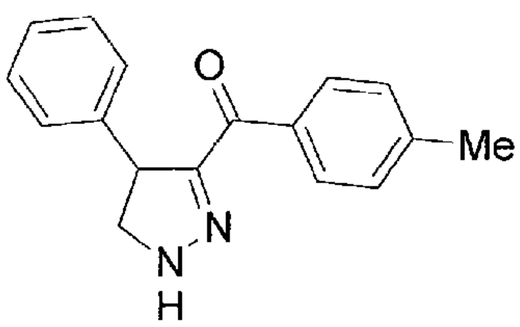
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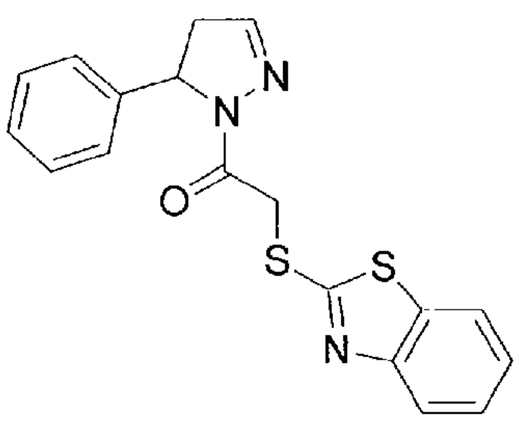
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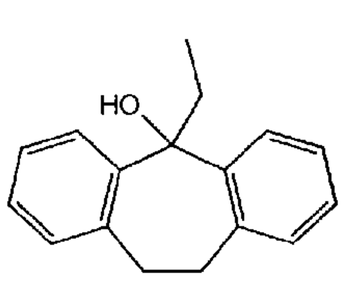
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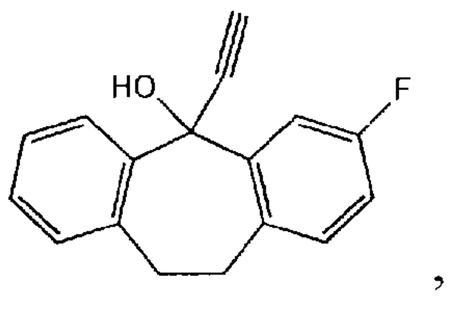
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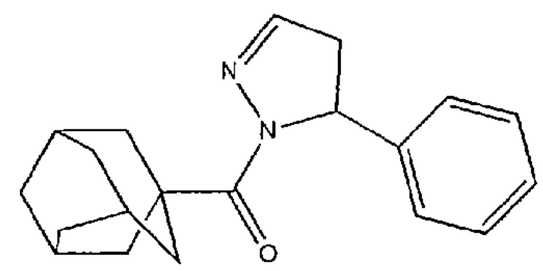
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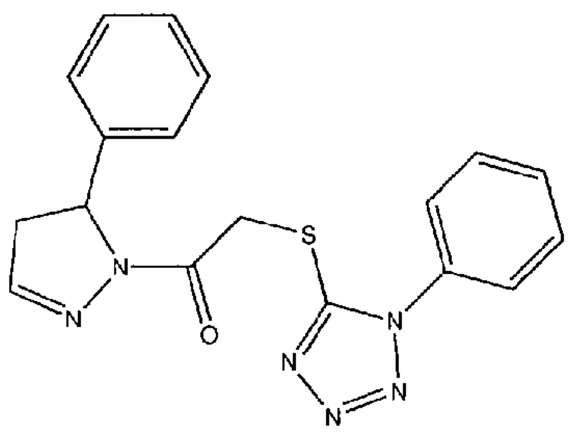
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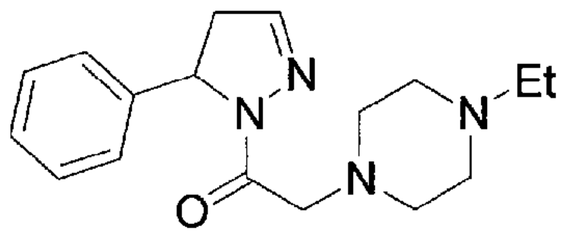
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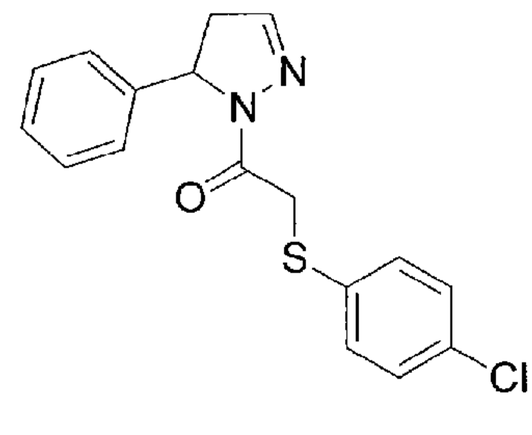
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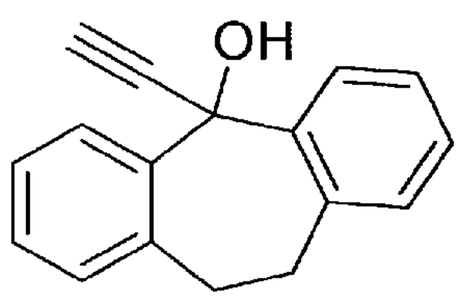
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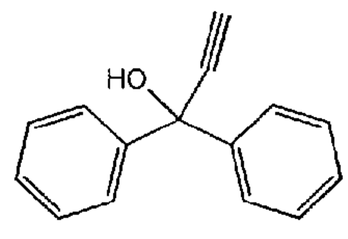
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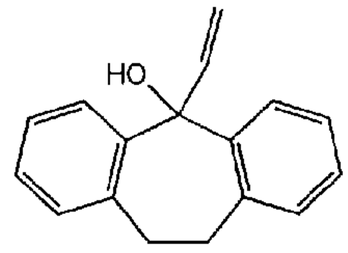
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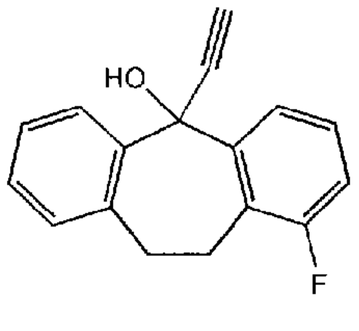
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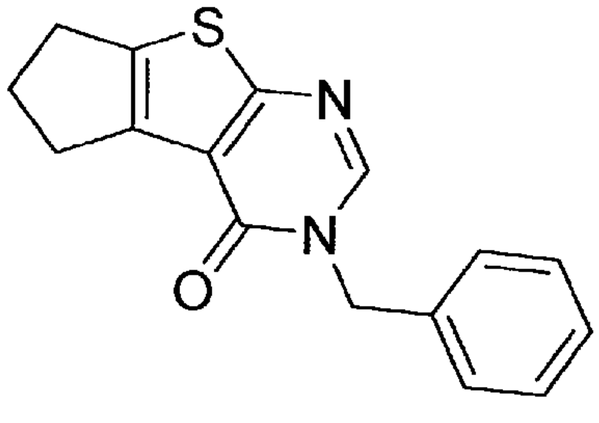
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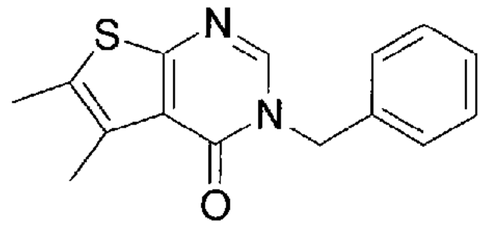
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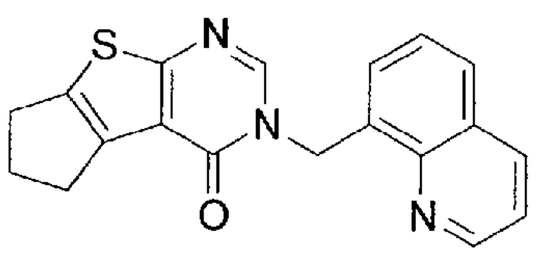
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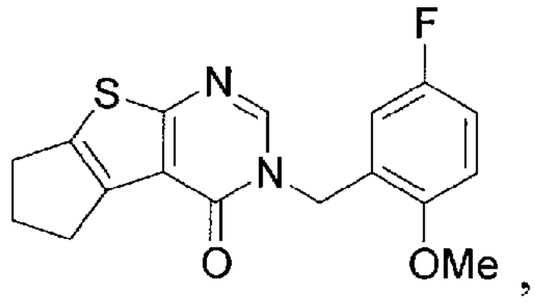
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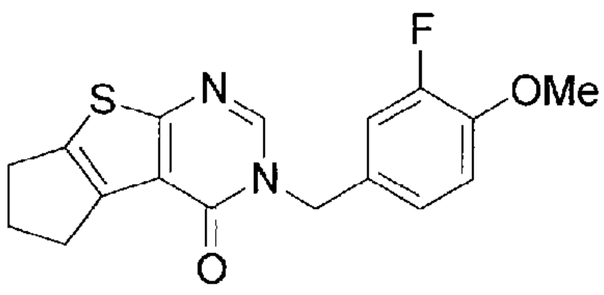
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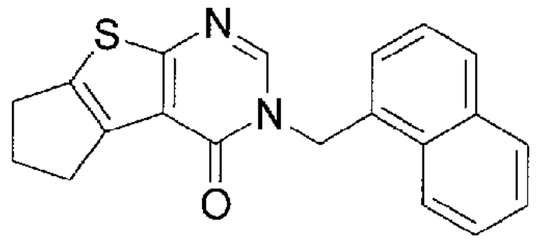
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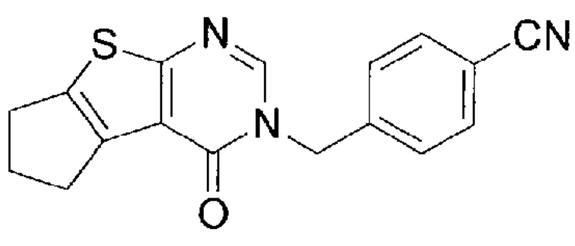
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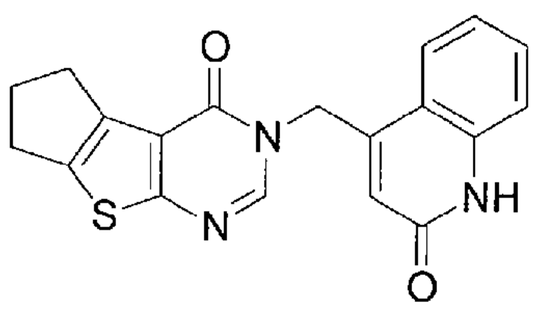
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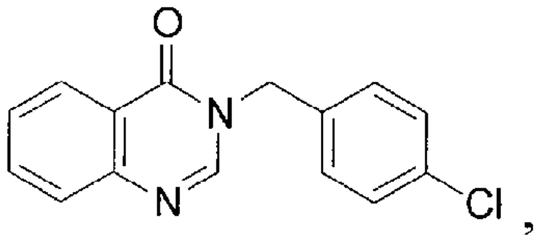
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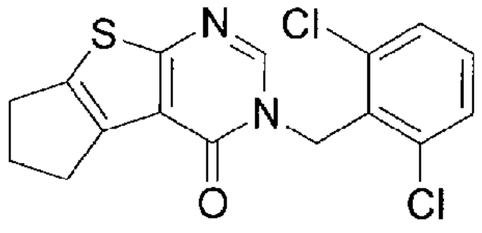
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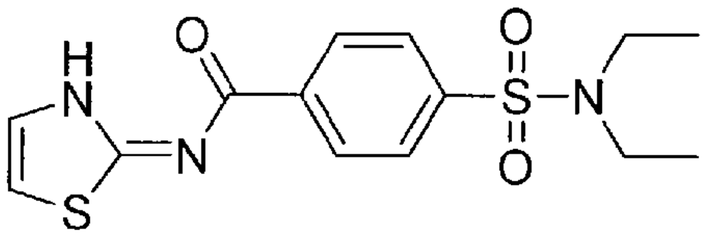
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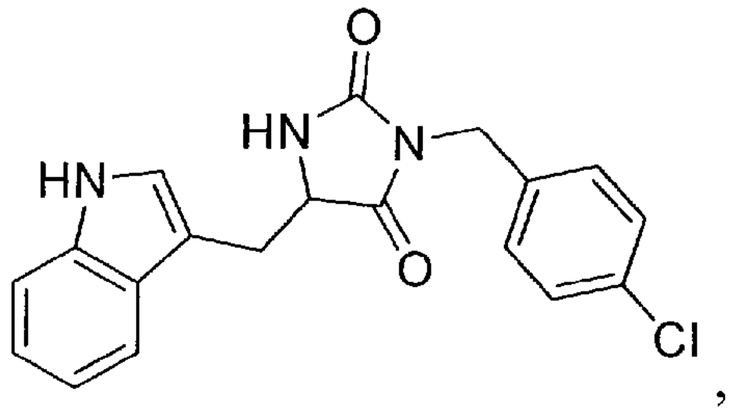
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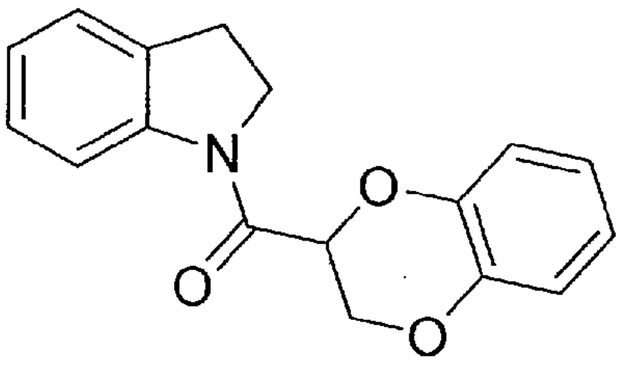
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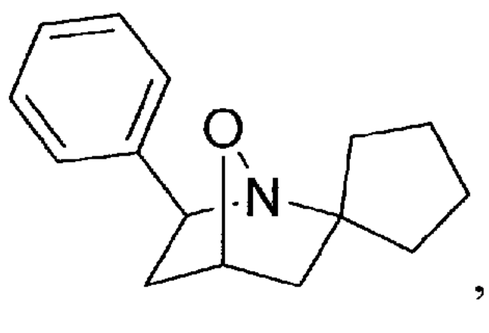
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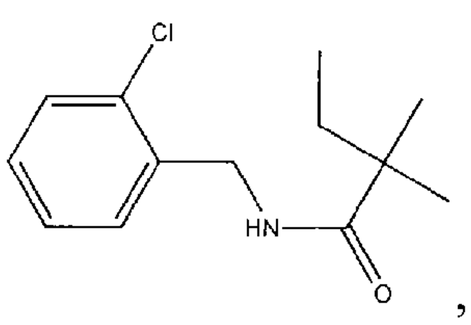
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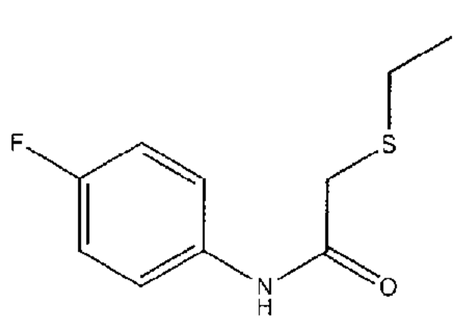
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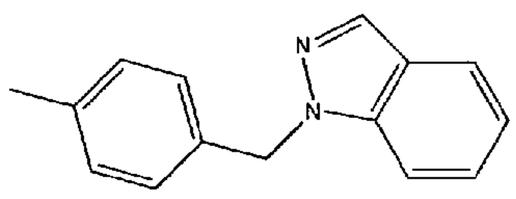
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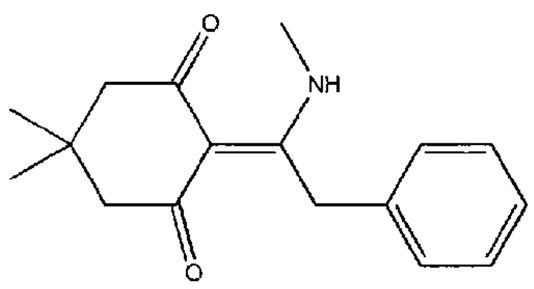
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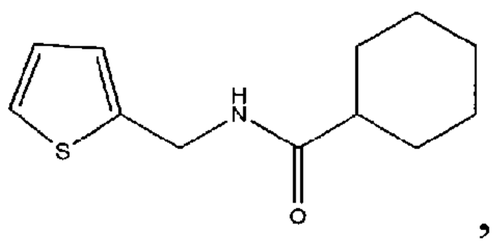
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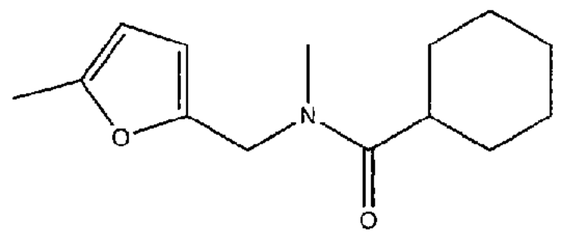
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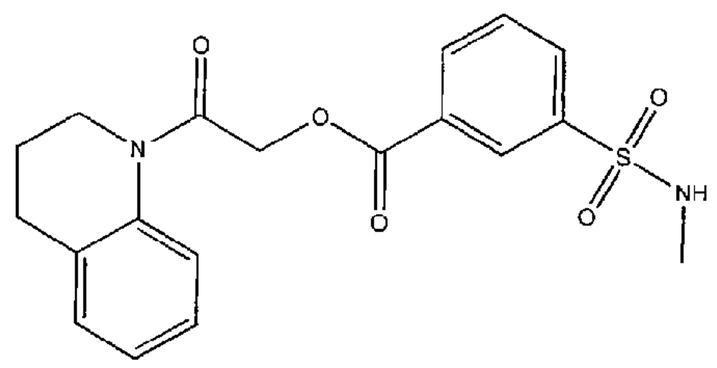
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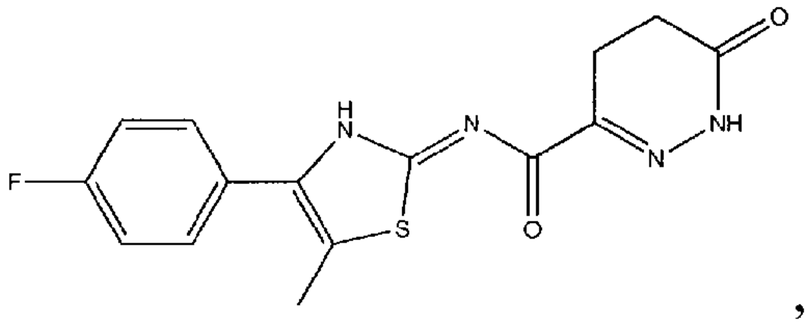
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